Title: Randomized controlled trial assessing transperineal prostate biopsy to reduce infection complications

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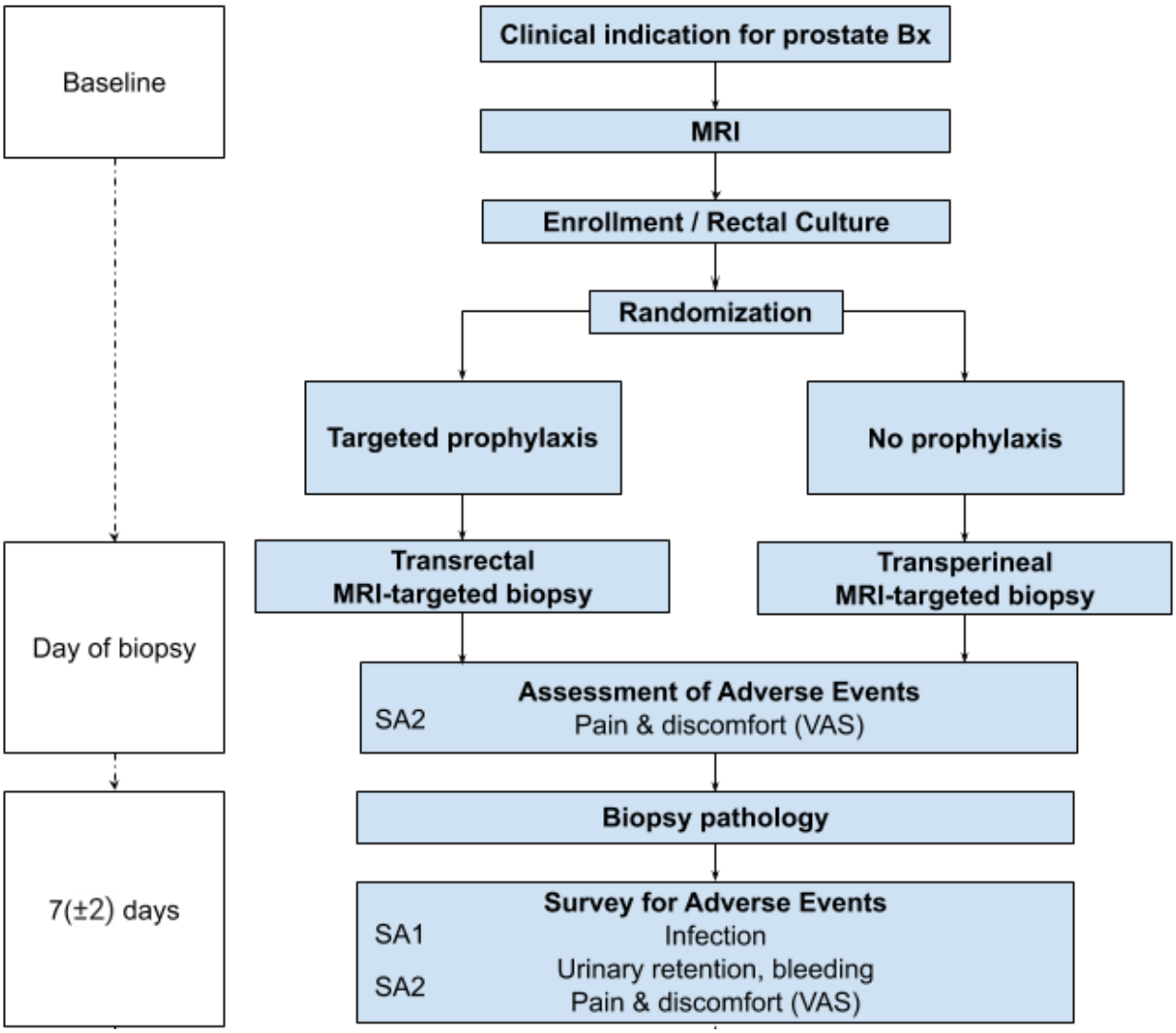
Protocol Summary

Full Title:	*Randomized controlled trial assessing transperineal prostate biopsy to reduce infection complications*
Clinical Phase:	*II*
Principal Investigator:	*Jim C. Hu, M.D., M.P.H.*
Sample Size:	*N= 1,702*
Study Population:	*Men who are aged at least 18 years with: history of Grade Group 1 or 2 prostate cancer, first diagnosed prior to date of planned biopsy (active surveillance cohort); clinical concern for the presence of prostate cancer as determined by the treating urologist and prior negative prostate biopsy performed ≤36 months prior to date of planned biopsy (prior negative cohort); Men without previous prostate biopsy (first time prostate biopsy)*
Accrual Period:	*Approximately 31 months*
Study Design:	*Prospective, randomized trial with 1:1 ratio to either the transperineal or transrectal biopsy group. Participants will be assessed for adverse events, pain and discomfort immediately and 7 days post-biopsy.*
Intervention Description:	*Transrectal prostate biopsy (TR-Bx) under local anesthesia is currently the most commonly used approach to evaluate for the presence of prostate cancer. A limitation of TR-Bx is the need for biopsy needles to pass through the rectal mucosa on their trajectory to the prostate, placing men at high risk of an infectious complication. An alternative method for performing prostate biopsy is via a percutaneous transperineal approach. One limitation of transperineal prostate biopsy (TP-Bx) has been the historic need for it to be performed under general or spinal anesthesia in order for patients to tolerate the multiple required needle passes through the perineal skin. Due to recent technical advances TP-Bx may now be safely performed under local anesthesia.*
Primary Objective:	*To compare infection adverse events of TP-Bx vs. TR-Bx performed under local anesthesia.*
Secondary Objectives:	*To compare other adverse events such as bleeding and urinary retention. To compare detection rates of clinically significant and insignificant prostate cancer.*

SCHEMA



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1. Study Objectives

Primary Objective: The primary objective of this study is to compare the incidence and severity of infectious complications between the transperineal and transrectal approaches to prostate biopsy.

Secondary Objectives: Secondary objectives of this study include comparing the incidence of other adverse events, associated pain, and cancer detection rates between the transperineal and transrectal approaches.

2. Background

Approximately one million transrectal prostate biopsies (TR-Bx) are performed annually in the United States.[1] The number of prostate Bx is expected to increase due to the demographic growth of the aging male population. Moreover, 44% of U.S. men undergoing initial biopsy report having a repeat biopsy within five years.[2] Additionally, more than half of men diagnosed with prostate cancer currently opt for active surveillance, which requires serial repeat biopsy to monitor for disease progression.[3] Therefore, biopsy use will only increase with greater adoption of active surveillance and the greater number of aging men. The safety and effectiveness of this common procedure will impact 1 out of 3 U.S. men at least once during their lifetimes when they undergo biopsy.

Due to the need for biopsy needles to pass through the rectal mucosa on their trajectory to the prostate, TR-Bx is associated with a significant risk of infectious complications. The needle travels through the “dirty” rectal mucosa to the “clean” prostate at least 12 times,[4] and fecal flora may seed the vascular prostate gland and bloodstream, leading to infection.[5,6] One systematic review suggests this rate may be as high as 5%.[7] The United States Preventive Services Task Force (USPSTF) Grade C recommendation for PSA screening considered adverse events associated with biopsy among the harms of PSA-based screening.[8] Despite antibiotic prophylaxis, 44% of men experience bacteriuria and 16% experience bacteremia after TR-Bx.[9]

Furthermore, the risk of post-biopsy infection has increased in recent years due to the growing incidence of antibiotic resistance.[10] Nam first reported an alarming four-fold, population-based increase in post-Bx infection hospital admissions from 0.6% in 1996 to 3.6% in 2005 among 75,190 patients.[11] In particular, men with fluoroquinolone-resistant bacteria in the rectum are at increased risk for post-Bx infection and sepsis,[12] which can result in dire complications such as limb gangrene/amputation, endocarditis, meningitis, disseminated intravascular coagulation (DIC) or death.[13–18]

As an alternative to the transrectal approach, prostate biopsy may be performed percutaneously through the perineal skin. Due to avoidance of the rectum, transperineal prostate biopsy (TP-Bx) is associated with an overall lower risk of infectious complications. At some centers, this has obviated the need for perioperative antibiotics, which is reinforced by the Society of Interventional Radiology Guidelines. [19,20] One additional benefit of TP-Bx is that this procedure offers better sampling of the anterior prostate, which is missed with the transrectal approach in men with larger prostate volumes due to benign prostatic hyperplasia.[21] The biopsy core excursion is 2 cm, and therefore sampling of the anterior prostate from the rectum is limited. In contrast, the TP approach has relative ease of access to the anterior prostate.[6] This is reflected

in greater detection of clinically significant prostate cancer in retrospective studies with transperineal[22–25] under general anesthesia (49%-91%) vs. transrectal[24,26–31] Bx approaches (14-42%). Given more than 80% of first-time biopsy nationally are performed without MRItargeting,[32,33] the utility of in-office transperineal vs. transrectal MRI-targeted biopsy must be evaluated as this applies to a large population of men. For instance, the American Urological Association professional guidelines were updated to recommend MRI use for first-time biopsy in early 2020;[34] however, lack of insurance coverage and limited access for urologists to the costly MRI-targeted biopsy platform contribute to a large population of men who need to be evaluated in the repeat biosy setting of active surveillance and prior negative biopsy.

Despite the aforementioned benefits of TP-Bx, this procedure has seen limited adoption due to the historic need for it to be performed under general anesthesia in order for patients to tolerate the required multiple needle sticks to the perineal skin. Additionally, because of the need for biopsy needles to traverse the pelvic floor muscles and vascular prostate apex, TP-Bx is believed to have a higher risk for urinary retention and bleeding as compared to the traditional transrectal approach.

In recent years, the development of novel local anesthetic techniques and needle guides has permitted TP-Bx to be performed in the office setting with a more favorable side-effect profile.[20,35,36] There has, however, been slow adoption of this procedure by only a handful of centers. In fact, national estimates of TP-Bx use place this figure closer to approximately 1-2%.

In this study, we aim to compare the safety, tolerability, and cancer detection rates of TP-Bx versus TR-Bx within the contexts of a randomized clinical trial. The results of this study will provide high level medical evidence regarding which method of prostate biopsy carries the best risk to benefit ratio for men undergoing evaluation for prostate cancer.

3. Subject Selection

3.1 Study Population

This study will include all men who are recommended to undergo prostate biopsy as part of routine clinical care. Inclusion and exclusion criteria are listed in the following sections.

3.2 Inclusion Criteria

- Male sex
- Age ≥18 years
- Active surveillance cohort: History of Grade Group 1 or 2 prostate cancer, first diagnosed prior to date of planned biopsy
- Prior negative cohort: Clinical concern for the presence of prostate cancer as determined by the treating urologist and prior negative prostate biopsy ≤36 months prior to date of planned biopsy
- Men without previous prostate biopsy (first time prostate biopsy)
- Willingness to sign informed consent and adhere to the study protocol

3.3 Exclusion Criteria

- Acute prostatitis within the last 6 months
- PSA > 20 ng/mL in men who have previously undergone prostate biopsy
- Current non-urologic bacterial infection requiring active treatment with antibiotics
- Unfit to undergo prostate biopsy under local anesthesia

- Prior definitive therapy for prostate cancer, such as radiation therapy or partial gland ablation
- Men who have previously undergone prostate biopsy in whom artifact would reduce quality of prostate MRI (extensive orthopedic pelvic metal)
- Contraindication to prostate MRI (claustrophobia, pacemaker, chronic kidney disease) in men who have previously undergone prostate biopsy

4. Study Procedures

4.1 Study Enrollment and Randomization

Eligible patients will be informed of the study by the study urologist and research staff. Interested participants may also learn more about the study through online resources such as ClinicalTrials.gov or through study informational brochures. All potential subjects will be allowed as much time as needed to consider study participation. Patients choosing to participate in the study will be consented within the privacy of a clinical exam room. Study staff will explain to each potential subject the research objectives, risks and benefits of study participation, and the subjects' rights and responsibilities. For patients who are scheduled for biopsy, electronic consent will also be available via phone. Eligible patients will be contacted by a member of the study team (i.e. investigator or research coordinator), who will explain the study to the patient. The patient will also receive a link to the electronic consent form via email or MyChart message.

This study will utilize either a traditional one-stage or a two-stage consent process. The reason for having the one-stage consent is there are a few sites in which the predominant approach is transperineal. Therefore, this two-stage consent does not work. With the one-stage consent, patients give permission to participate in the study prior to randomization (tradtional RCT consent). With a second-stage consent, subjects who meet all eligibility criteria will sign the firststage consent form. Patients will have the option to sign the consent in person or electronically. First-stage consent will register the subject to the study and will allow investigators to use their data from their medical record and post-biopsy questionnaire responses for research purposes. Subjects who sign first-stage consent will be randomized in a 1:1 ratio to receive TP-Bx or TRBx. The patients' first-stage consent or their traditional one-stage consent will be valid for eight months to accommodate for biopsy scheduling. This will reduce the number of re-consents and align with the standard of care timeline for biopsy procedures. Biopsies are often scheduled as far out eight months from their clinic visit.

Participants will be consented remotely using an electronic version of the informed consent form that follows federal, state, and local regulations, as applicable. We will implement the following procedures for electronic informed consent.

The informed consent document(s) will be sent to the subject or their Legal Authorized Representative (LAR), if applicable, via secure email sent by REDCap prior to the scheduled consent discussion. The subject or LAR will be asked to review the consent document prior and during the consent discussion with a study staff member via phone or approved teleconferencing service (i.e., Zoom). The study staff member will confirm the subject or LAR has read and has the capacity to appreciate all aspects of the information presented in the consent process for the research study. The subject or LAR will be encouraged to ask questions. If agreeing to participate, the subject or LAR will sign the consent form using electronic informed consent (eConsent) via REDCap. A computer, tablet or touch screen phone will be used to capture digital signatures. The person conducting consent will also sign the electronic informed consent (eConsent) document in a contemporaneous manner. Subjects will

be provided with a digital copy of the completed form via email. The informed consent discussion and process will be documented by the study team in the subject's medical record or study record.

If a subject does not have access to a touch screen phone, computer or tablet, cannot work with remote electronic informed consent, or the remote electronic informed consent cannot be obtained for any other reasons, the consent may be conducted and documented at an in-person visit prior to study activities via paper consent form or through REDCap on an ITS tagged device.

The assignment sequence will use randomly permuted blocks of unequal size stratified by urologist, PSA (<4, 4-9.9, ≥10 ng / mL) and biopsy indication (prior negative vs. active surveillance) and implemented by the randomization model in REDCap, which prevents an investigator from learning allocation before a patient is unambiguously registered on study and from changing allocation afterwards, thus ensuring full allocation concealment. For men with prior biopsy, we exclude men with a PSA >20 ng/mL.

For the REDCap randomization model, randomization of subjects will occur on the data collection form where the randomization field is located. Before a subject is randomized, a 'Randomize' button will appear next to that field. When a user (who has been given appropriate 'Randomize' user privileges) clicks that button, a pop-up box will appear that will allow the user to randomize the subject. After a subject has been randomized, the grouping (i.e. transrectal or transperineal biopsy) will become permanently locked and unmodifiable. The randomization field will always be locked and unmodifiable both before and after randomization has occurred for a subject.

Randomization is unblinded, and research coordinators of respective enrolling sites will inform their patients of the assigned cohort.

Subjects randomized to TR-Bx will receive transrectal biopsy. Subjects randomized to TP-Bx will undergo a second consent discussion with the enrolling investigator, where the risks and benefits of transperineal biopsy will be explained. Subjects can then decide whether to undergo standard transrectal biopsy or transperineal biopsy. Subjects who agree to undergo TP-Bx will sign the second-stage consent form.

4.2 Data Collection & Confidentiality

Study data will be prospectively collected from patient medical records and patient surveys. In all participating centers, the site-specific research coordinator will perform baseline data acquisition and medical record abstraction. This data will be entered into standardized clinical report forms housed within a REDCap environment and hosted by WCM. Each patient will be assigned a unique study identifier.

REDCap (Research Electronic Data Capture) is a secure, web-based application designed exclusively to support data capture for research studies. The REDCap platform will be partitioned to permit read/write access only to site-specific records such that individual sites will be able to access records for their own subjects, exclusively. REDCap has a secure email and web-based data collection interface that may be utilized for collecting data. The site-specific research coordinator will determine individual patients' preferred method of survey response

and may collect survey data either through mail, telephone, REDCap, or during an in-person visit.

Only the WCM research coordinator will be able to review de-identified data across sites to conduct data quality checks and share data quality with the study biostatistician.

To ensure accuracy of data entered in the REDCap database from source documents (including surveys and medical record abstract), sites will perform 100% visual review and conduct double data entry for a sample (i.e., 10%) of the data.

Data quality checks will be conducted every 6 months, coinciding with Data Safety and Monitoring reviews.

For protocol deviations fitting immediately reportable criteria, the DSMC's primary concern lies with whether the deviation has the potential to negatively impact subject safety or integrity of study data or whether the deviation places subjects at greater risk of harm (including physical, psychological, economic or social harm). If the DSMC makes determinations that the reported protocol deviation impacts either, it may recommend modifications, suspension or termination of the study.

Interim study findings will be communicated in cases where modifications are recommended. The DSMC will require the PI to submit confirmation to the DSMC that the modification(s) have been made, or to submit a reason why the PI did not agree with the DSMC's recommendation.

4.3 Study Calendar

	Month -8 to Day 0	Day 0	Day 5 to 9
Eligibility	X[a]		
Informed consent	X		
Demographics	X		
Medical history[b]	X		
Physical exam[c]	X		
Randomization	X		
PSA	X		
Rectal swab[d]	X		
Prostate Biopsy		X	
Assessment of Adverse Events[e]			X
Concomitant Medications[f]		X	X

[a]To be performed prior to informed consent. [b]Medical comorbidities, indication for biopsy, multiparametric MRI findings, and history of prior biopsy or infection. [c]Height and weight. [d]for transrectal biopsy only.
[e]Assessed by patient questionnaire. Events will be grading using Common Terminology Criteria for Adverse Events (CTCAE) v5.0. [f]Assessed by patient quaestionnaires.

4.4 Antibiotic Administration

For patients undergoing a TR-Bx, antibiotic prophylaxis will be administered in accordance with guidelines from the American Urological Association (AUA).[37] No antibiotic prophylaxis will be administered for patients undergoing a TP-Bx.

4.5 Biopsy Procedure

A meeting of study investigators will take place before recruitment to review and ensure standardization of biopsies approaches. Investigators will follow the technique described by Kubo et al. to administer lidocaine during TP-Bx.[20] For both transperineal and transrectal approaches, 20 mL of 1% lidocaine will be used, respectively, to standardize local anesthesia. At each site, however, the choice of commercial MRI-targeted biopsy platform will be left to the physicians' discretion.

In both transperineal and transrectal biopsy arms for MRI-targeted biopsy, the number of systematic biopsy cores will be standardized to 12 cores. The technique for TR-Bx is performed as described by Kasivisvanathan et al.[22] A total of 12 systematic biopsy cores will be obtained from the peripheral zone of the prostate at the base, mid gland, and apex. Locations of the 12 systematic cores are: Right lateral base, Right lateral midgland, Right lateral apex, Right medial base, Right medial midgland, Right medial apex, Left lateral base, Left lateral midgland, Left lateral apex, Left medial base, Left medial midgland, and Left medial apex. The technique for TPBx is performed as described by Urkmez et al.[38]. Locations of the systematic cores will be obtained as follows: 2 cores each at Right posterior lateral, Right posterior medial, Left posterior lateral, and Left posterior medial, as well as 1 core each at Right anterior lateral, Right anterior medial, Left anterior lateral, and Left anterior medial.

In both transperineal and transrectal biopsy arms, the number of targeted biopsy cores will be standardized to 3 cores per target, with a maximum of three ROIs permitted to be chosen for targeted biopsy. MRI-targeted biopsy registration (i.e., matching of the image of the target on MRI with the real-time image of the prostate during biopsy) may be performed by means of visual registration or software-assisted registration.

De-identified video capture of each site's first 10 TP-Bx and TR-Bx will be distributed for review among investigators to monitor for variation in biopsy technique. Deviations from the technique that may occur during routine clinical care will be recorded for each case, monitored by the WCM DSMC and compared between groups. Research coordinators at each site will randomly select 3 TP-Bx and 3 TR-Bx for video upload every 3 months. Investigators will review and discuss during quarterly video-conferences to ensure consistent procedural fidelity throughout the study.

4.6 Duration of Follow Up

Patients will be followed for approximately 7 days following biopsy to evaluate for adverse events. Subjects experiencing an adverse event beyond 7 days stabilization will be followed until resolution or stabilization.

5. Measurement of Outcomes

5.1 Adverse events

The primary objective of this study is to compare the incidence and severity of infectious complications experienced by patients undergoing TP-Bx versus TR-Bx. Patients will be assessed for complications by way of electronic questionnaire administered 7±2 days post biopsy using a REDCap site hosted at Weill Cornell Medical Center. For patients unable to complete the questionnaire electronically, responses will be obtained via telephone interview. Any patient indicating that they experienced an adverse event will be contacted by the study team to seek further details. Additionally, all relevant medical records will be requested. Adverse events will be classified in accordance with Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

The primary outcomes are infection rates of TP-Bx versus TR-Bx.
The secondary outcomes are patient-reported pain and anxiety, and comparison of noninfectious complications such as bleeding and urinary retention rates, and cancer detection.

Timing for assessment of study variables.

Assessment	**Baseline Pre-Bx**	**Day of Bx**	**7-days Post-Bx**
Baseline history and physical exam, screening, consent	✓		
Prior Bx (Y/N)	✓		
Prior Bx infection (Y/N)	✓		
PSA	✓		
Indication for Bx	✓		
MpMRI findings	✓		
Randomization: TR-Bx vs. TP-Bx	✓		
Bx infection risk determination for TR-Bx prophylaxis	✓		
Bx completed (Y/N)		✓	
Bx duration (minutes)		✓	
Pain (VAS)		✓	✓
Discomfort (VAS)		✓	✓
TMI Anxiety (Likert 5 levels)		✓	
Decision regret			✓
Adverse events (Y/N) and Bother			
UTI			✓
Sepsis			✓
Urinary retention			✓

Fever	✓
Hematuria	✓
Hematochezia	✓
Hematospermia	✓
UTI diagnosed by HCP	✓
Unplanned HCP contact	✓
Qualitative responses	✓
Bx pathologic outcomes, if cancer:	✓
Gleason grade group(s)	✓
Number of cores positive	✓
Number of cores negative	✓
Maximum cancer core length	✓
Targeted Bx positive (Y/N/NA)	✓
Systematic Bx positive (Y/N)	✓
Location of positive cores	✓

5.2 Pain, Anxiety and Discomfort

A questionnaire will be given to patients immediately after the biopsy and at 7±2 days post-biopsy (Appendix). The questionnaire captures discomfort and pain and fear-anxiety using a numerical rating scale (0-10), with higher scores indicating greater intensity of symptoms. The questionnaire also asks about the presence or absence of adverse events, with reporting of significant adverse events (fever, chills, urinary retention, urinary tract infection, treatment from a doctor) subject to follow-up from study staff.

Infectious complications will be captured as: (1) uncomplicated urinary tract infection (UTI): dysuria, urgency, frequency or hematuria without fever and with or without pyuria (>5 white blood cells per high-powered field or positive leukocyte esterase on urine dipstick) or bacteriuria (≥ 105 colony-forming units/mL); (2) complicated UTI: fever, flank pain, nausea or vomiting with or without pyuria and bacteriuria; (3) urosepsis: criteria for sepsis, severe sepsis, and septic shock[39] were combined and categorized as urosepsis.[40]

5.3 Biopsy Pathology

The proportion of men diagnosed with clinically significant cancer and clinically insignificant cancer will be compared by biopsy approach. Detection of prostate cancer will be captured from the final pathology report. We will record the prostate cancer grade, number and location of positive biopsies for transrectal (location: left vs. right, medial vs. lateral, apex, mid, and base) and for transperineal (location: posterior medial, posterior lateral, and anterior), as well as the maximum cancer core length (in mm), and total number of negative cores. In order to compare outcomes, prostate cancer grade will be categorized into insignificant (Gleason grade group 1) and clinically significant (grade group ≥ 2).[22]

6. Statistical Considerations

We define infection complication as any of the following: (1) fever requiring medical advice or intervention; (2) chills requiring medical advice or intervention; or (3) UTI diagnosed by healthcare professional.[41] We aim to enroll 1,702 (n=682 active surveillance, n=620 prior negative biopsy, n =400 first time biopsy) subjects in this study, with equal randomization between groups. We assume that the infection rate in the transperineal group is 0.5%. Given a one-sided α of 0.10, the power to reject the null hypothesis of no difference in infection rates will be >80% if the event rate in the transrectal group is 2.0%. The event estimate is consistent with published post-transrectal biopsy infection rates range from 1% to 17.5%[41–49] and the 2017 AUA prostate biopsy guidelines cite an infection risk of 5-7%.[37]

Analysis of infection, detection of clinically significant cancer (i.e. Grade Group 2+), over-detection of clinically insignificant cancer (i.e. Grade Group 1), presence vs. absence of other biopsy related complication grade 2 or above and, separately, Grade 1 (patient-reported hematuria, hematospermia or hematochezia) will be by logistic regression with site and prior negative vs. active surveillance as fixed effect covariates. The Barnard's test will be used to analyze the data. Absolute risk differences will be calculated by applying the odds ratio from the regression to the prevalence in the transrectal group, with 95% CI obtained by bootstrapping. As a sensitivity analysis for high-grade cancers missed on biopsy, we will include as an event any detection of grade group ≥2 cancer up to two years after randomization, whether detected by subsequent biopsy or upgrading on surgical pathology, as a binary variable. We will also explore whether the relative effects of transperineal biopsy on cancer detection varies by race or diagnostic setting (active surveillance vs. prior negative) by adding race (African ancestry yes or no) or setting (active surveillance vs. prior negative) and the associated interaction terms in two separate logistic regression models.

Rates of missing data are expected to be extremely low because all outcomes are assessed within a short period of time after biopsy. Hence, we do not anticipate having to use statistical methods to handle missing data. However, if rates of missing data are more than 5%, we will implement multiple imputation using chained equations.

To compare the detection of clinically significant cancer biopsy with systematic vs. MRI-targeted biopsy, stratified by transperineal vs. transrectal, the analyses will be conducted separately for the prior negative biopsy and active surveillance cohorts separately. For the prior negative biopsy patients, we will create a model with the outcome of clinically significant cancer and predictors of the linear predictor from the standard Prostate Biopsy Collaborative Group model plus PI-RADS version 2 MRI score and MRI prostate volume.[50] For the active surveillance cohort, we will use a similar approach but use the Canary “base” model for biopsy outcome in active surveillance patients.[51] We will report the increase in discrimination associated with using MRI volume and PIRADS score and conduct decision curve analysis, a decision-analytic technique that weighs the value of avoiding unnecessary biopsy compared to missing high-grade cancer, to assess the clinical utility of the models.[52]

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APPENDIX

Immediate post biopsy questionnaire

Please ask the patient to fill this out after the biopsy, before they leave the department.

Please check the box corresponding to the number, which describes how you felt immediately after the biopsy procedure:

1. Overall, how much **discomfort** did the biopsy procedure cause you?

0	1	2	3	4	5	6	7	8	9	10

No discomfort — Moderate discomfort — Extreme discomfort

2. Overall, how much **pain** did the biopsy procedure cause you?

0	1	2	3	4	5	6	7	8	9	10

No pain — Moderate pain — Extreme pain

3. Overall, how much **fear/anxiety** did the biopsy procedure cause you?

0	1	2	3	4	5	6	7	8	9	10

No fear or anxiety — Moderate fear or anxiety — Extreme fear or anxiety

4. Please list any medications that you are currently taking. An example is given in the first box:

Name of medication	**Dosage**	**Number of doses per day**	**Start Date**	**End Date**	**Indication**
e.g. ciprofloxacin	*500mg*	*2*	*09/29/2021*	*10/06/2021*	*Infection*

Thank you for completing the questionnaire. Please hand this to the research 7-day post biopsy questionnaire

1. Overall, how much **discomfort** do you have from the biopsy?

0	1	2	3	4	5	6	7	8	9	10

No discomfort — Moderate discomfort — Extreme discomfort

2. Do you have pain at the site where the biopsy was taken?

Yes ☐ No ☐

3. If Yes, how much **pain** are you having at the biopsy site?

0	1	2	3	4	5	6	7	8	9	10

No pain — Moderate pain — Extreme pain

Did you experience the following problems during the 7 days after the biopsy procedure?

1. Fevers

Yes ☐ No ☐

2.Shivering and/or chills, as if you had a flu

Yes ☐ No ☐

3.Blood in the urine (“pee”)

Yes ☐ No ☐

4.Blood in the semen (ejaculate or “cum”)

Yes ☐ No ☐

5. Blood in the stools (“poop”)

Yes ☐ No ☐

6. Acute urinary retention, meaning being unable to pass urine (“pee”) which was relieved by putting a catheter into the bladder through the penis

Yes ☐ No ☐

7. Urinary tract infection diagnosed by a healthcare professional (doctor or nurse)

Yes ☐ No ☐

8. Please list any new medications, especially any painkillers or antibiotics, that you have taken since the biopsy. Do not list your regular medications but do list any new medications started related to the biopsy. Only list the medications if you have taken them. An example is given in the first box:

Name of medication	**Dosage**	**Number of doses per day**	**Number of days**

e.g. ciprofloxacin	*500mg*	*2*	*3*

9. Since the biopsy, have you had contacts with hospital services for reasons related to the biopsy, which were unplanned and not part of the routine study visits?
   Please answer yes if you have had any unplanned contact with any healthcare staff e.g. doctor, nurse, other. Please also answer yes if you have had any unplanned consultations with healthcare staff over the phone:

   Yes ☐ No ☐

10. Since the biopsy, have you had contacts with the community healthcare team for reasons unrelated to the biopsy?
    Please answer yes if you have had any contact with any healthcare staff in the community e.g. GP, practice nurse, community nurse, other. Please also answer yes if you have had any consultations with community healthcare staff over the phone:

    Yes ☐ No ☐

Thank you for completing the questionnaire. Please contact us if you have any questions.