5-19-2023

Protocol of a Multicentre Randomised Controlled Trial Assessing Transperineal Prostate Biopsy to Reduce Infectiouscomplications

Jim Hu

Alec Zhu

Andrew Vickers

Mohamad Ezzeddine Allaf

Behfar Ehdaie

See next page for additional authors

Authors

Jim Hu, Alec Zhu, Andrew Vickers, Mohamad Ezzeddine Allaf, Behfar Ehdaie, Anthony Schaeffer, Christian Pavlovich, Ashley E. Ross, David A. Green, Gerald Wang, Serge Ginzburg, Jeffrey S. Montgomery, Arvin George, John N. Graham, Benjamin T. Ristau, Andres Correa, Jonathan E. Shoag, Keith J. Kowalczyk, Tenny R. Zhang, and E.M. Schaeffer

BMJ Open

Protocol of a multicentre randomised controlled trial assessing transperineal prostate biopsy to reduce infectious complications

Jim Hu,[1] Alec Zhu ,[1] Andrew Vickers,[2] Mohamad Ezzeddine Allaf,[3] Behfar Ehdaie,[2] Anthony Schaeffer,[4] Christian Pavlovich,[3] Ashley E Ross,[4] David A Green,[1] Gerald Wang,[1] Serge Ginzburg,[5] Jeffrey S Montgomery,[6] Arvin George,[6] John N Graham,[1] Benjamin T Ristau,[7] Andres Correa,[8] Jonathan E Shoag,[9] Keith J Kowalczyk,[10] Tenny R Zhang,[1] EM Schaeffer[4]

To cite: Hu J, Zhu A, Vickers A, *et al*. Protocol of a multicentre randomised controlled trial assessing transperineal prostate biopsy to reduce infectious complications. *BMJ Open* 2023;**13**:e071191. doi:10.1136/bmjopen-2022-071191

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-071191).

JH and AZ are joint first authors.

Received 17 December 2022
Accepted 28 April 2023

For numbered affiliations see end of article.

Correspondence to
Dr Jim Hu;
jch9011@med.cornell.edu

ABSTRACT

Introduction Approximately one million prostate biopsies are performed annually in the USA, and most are performed using a transrectal approach under local anaesthesia. The risk of postbiopsy infection is increasing due to increasing antibiotic resistance of rectal flora. Single-centre studies suggest that a clean, percutaneous transperineal approach to prostate biopsy may have a lower risk of infection. To date, there is no high-level evidence comparing transperineal versus transrectal prostate biopsy. We hypothesise that transperineal versus transrectal prostate biopsy under local anaesthesia has a significantly lower risk of infection, similar pain/discomfort levels and comparable detection of non-low-grade prostate cancer.

Methods and analysis We will perform a multicentre, prospective randomised clinical trial to compare transperineal versus transrectal prostate biopsy for elevated prostate-specific antigen in the first biopsy, prior negative biopsy and active surveillance biopsy setting. Prostate MRI will be performed prior to biopsy, and targeted biopsy will be conducted for suspicious MRI lesions in addition to systematic biopsy (12 cores). Approximately 1700 men will be recruited and randomised in a 1:1 ratio to transperineal versus transrectal biopsy. A streamlined design to collect data and to determine trial eligibility along with the two-stage consent process will be used to facilitate subject recruitment and retention. The primary outcome is postbiopsy infection, and secondary outcomes include other adverse events (bleeding, urinary retention), pain/discomfort/anxiety and critically, detection of non-low-grade (grade group ≥2) prostate cancer.

Ethics and dissemination The Institutional Review Board of the Biomedical Research Alliance of New York approved the research protocol (protocol number #18-02-365, approved 20 April 2020). The results of the trial will be presented at scientific conferences and published in peer-reviewed medical journals.

Trial registration number NCT04815876.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is a multicentre, prospective randomised clinical trial with a large sample size that will compare the safety and efficacy of MRI-targeted transperineal versus transrectal prostate biopsy.
⇒ Trial results will generate multiple clinically relevant outcomes including postbiopsy infections rates and detection of non-low-grade prostate cancer.
⇒ Study sites will use a two-stage consent process to facilitate clinical study enrolment.
⇒ Medical record review and patient questionnaires will capture postbiopsy infection outcomes and other adverse events.
⇒ Although steps will be taken to ensure a standardised procedure protocol, small variation in procedure technique may occur among providers at different participating study sites.

INTRODUCTION

Approximately one million transrectal prostate biopsies are performed annually in the USA.[1] The number of prostate biopsies performed is expected to increase with an ageing population. Moreover, 44% of US men undergoing initial biopsy report having a repeat biopsy within 5 years,[2] and half of men diagnosed with low-risk prostate cancer opt for active surveillance, which requires serial biopsies to monitor for disease progression.[3] Ultimately, prostate biopsy and its accompanying benefits and risks will impact one out of three US men during their lifetimes.

Transrectal prostate biopsy is associated with a significant risk of infectious complications. Due to the trajectory of biopsy needles passing from the rectum into the prostate, which occurs at least 12 times in a systematic biopsy,[4] faecal flora may seed the prostate gland and bloodstream, leading

to infection.[5 6] Without antibiotic prophylaxis for transrectal biopsy, rates of bacteriuria and bacteraemia are 44% and 16%, respectively.[6] Even with prophylaxis, the rate of symptomatic infection—urinary tract infection or sepsis—after transrectal biopsy may be as high as 5%.[7] In making its grade C recommendation for prostate-specific antigen (PSA) screening, the US Preventive Services Task Force considered adverse events associated with biopsy among the harms.[8]

The risk of postbiopsy infection increased in recent years due to growing antibiotic resistance.[9] Nam *et al* first reported an alarming fourfold population-based increase in hospital admissions due to post-Bx infection from 0.6% in 1996 to 3.5% in 2005 among 75 190 Canadian men.[10] More recently, Womble *et al* demonstrated hospital admission rates following prostate biopsy were predominantly due to infectious complications and ranged from 1% to 4% even though guideline-concordant antibiotics were administered in 96% of biopsies.[11] In particular, men with fluoroquinolone-resistant bacteria in the rectum are at increased risk for postbiopsy infection and sepsis,[12] which can result in dire complications such as limb gangrene/amputation, endocarditis, meningitis, disseminated intravascular coagulation or even death.[13–18] Additionally, Jiang *et al* evaluated 15 236 transrectal biopsy over 3 years and demonstrated a significant increase in fluoroquinolone-resistant bacteria on rectal swab cultures of 25%, 30% and 33% in years 1, 2 and 3, respectively.[19]

The American Urological Association (AUA) recommends administering fluoroquinolone antibiotic prophylaxis at least 1 hour prior to biopsy for up to 24 hours, and a single dose of antibiotics may be sufficient.[20] For higher-risk men, guidelines recommend targeted prophylaxis (rectal culture based), augmented prophylaxis (fluoroquinolone plus an additional antibiotic) or a transperineal approach. While targeted and augmented antibiotic prophylaxis may be superior to standard prophylaxis in preventing infectious complications, neither targeted nor augmented prophylaxis has shown superiority over each other.[19 21–23] Furthermore, Jiang *et al* noted that the use of augmented prophylaxis goes against recommendations for antibiotic stewardship by the Centers for Disease Control and Prevention due to increasing antibiotic resistance.[19]

As an alternative to the transrectal approach, prostate biopsy may be performed percutaneously through the perineal skin which avoids introducing bacteria into the prostate via the rectum. Multiple studies have demonstrated the transperineal approach, compared with the transrectal approach, contributes to reduced infectious complications.[24–26] While infectious complications after transperineal biopsy are possible, rates of infection are low even without the use of prophylactic antibiotics.[27–29] Therefore, the transperineal prostate biopsy can be performed without prophylactic antibiotics and is recommended by multiple guidelines.[20 30 31] An additional benefit of transperineal prostate biopsy is potentially superior sampling of the anterior prostate, which can be challenging to sample via the transrectal approach, especially in men with larger prostates due to the limited biopsy core excursion of only 2 cm.[32] The transperineal approach has relatively easy access to the anterior prostate,[33] which is reflected in greater detection of non-low-grade prostate cancer in retrospective studies comparing transperineal[34–37] under general anaesthesia (49%–91%) vs transrectal[36 38–43] biopsy approaches (14%–42%).

Although more than 80% of first-time biopsies in the USA are performed without MRI targeting,[44 45] recent evidence demonstrated the superiority of MRI-targeted biopsy compared with conventional ultrasound-guided biopsy in detecting more high grade prostate cancers.[46] However, MRI-targeted biopsy may lead to overtreatment, and the long-term benefits of targeted biopsy to reduce risk of metastasis and death are unclear.[47] Nevertheless, the AUA and European Association of Urology guidelines recommend prostate MRI in men who are biopsy-naïve and in those who have prior negative biopsies.[48 49] MRI-targeted versus ultrasound-guided biopsy has been studied almost exclusively using the transrectal biopsy, and the accuracy of MR targeting with transperineal biopsy remains understudied.[50]

Despite the benefits of transperineal prostate biopsy, there has been limited adoption historically as it was perceived to require general anaesthesia. In addition, due to needle passage through the pelvic floor muscles and the vascular prostate apex, transperineal prostate biopsy is believed to have a higher risk for urinary retention and bleeding than the traditional transrectal approach. Indeed, data from New York state as well as Surveillance, Epidemiology and End Results Programme-Medicare through 2015 demonstrate that 99% of prostate biopsies are still performed transrectally.[51] More recent data evaluating nearly 500 000 prostate biopsies performed from 2008 to 2019 within the National Health Service of the UK demonstrated around 20% of biopsies were performed via the transperineal approach.[52]

In recent years, novel local anaesthetic techniques and needle guides enabled transperineal prostate biopsy in the office setting.[53–55] In-office transperineal biopsy may be a transformative innovation that can eliminate postbiopsy infectious complications and lower healthcare costs by avoiding the need for general anaesthesia and ambulatory surgery centres. In addition, the ability to perform MRI-targeted transperineal biopsy in the office may allow better sampling with fewer individual biopsy cores than the traditional transperineal approach performed in the operating room.

High-level, prospective evidence demonstrating the best risk-to-benefit ratio for men undergoing prostate biopsy is lacking. We aim to compare the safety, tolerability and cancer detection rates of transperineal prostate biopsy versus transrectal prostate biopsy in a randomised clinical trial (RCT).

Traditionally, RCTs of surgical techniques have been difficult to execute. Clinical trials have been hindered by lack of research funding or inadequate infrastructures,

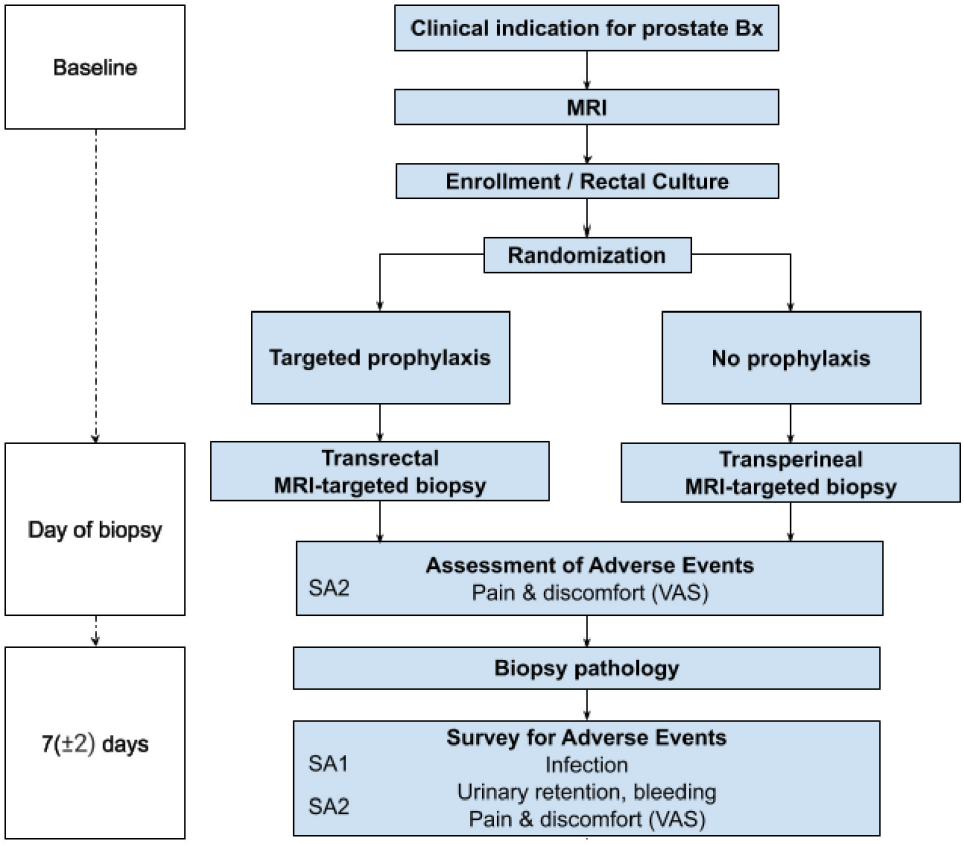

Figure 1 Consolidated Standards of Reporting Trials (CONSORT) diagram.

and various structural, cultural and psychological barriers exist that impede patient recruitment and randomisation to a surgical trial.[56 57] In addition, patient willingness to enrol in surgical RCTs depends on the treatment options and is higher when comparing surgical versus surgical interventions rather than surgical versus non-surgical interventions.[58] In order to improve the conduct of surgical trials, our study will use innovative recruitment techniques, such as the two-stage consent,[59 60] as well as a streamlined enrolment process that minimises patient burden in order to overcome some of the challenges of performing surgical RCTs.

METHODS AND ANALYSIS

Study design and setting

The study is a multicentre, randomised, controlled clinical trial performed across 10 academic medical institutions. Patients undergoing prostate biopsy for elevated PSA (biopsy-naïve or prior negative biopsies) or while on active surveillance will undergo systematic and MRI-targeted prostate biopsy and will be randomly assigned to transperineal or transrectal biopsy approach. Study participants will be assessed for infectious complications and other adverse events immediately and 7 days postbiopsy. Patients assigned to the transperineal biopsy group will receive no antibiotic prophylaxis, whereas those randomised to the transrectal biopsy group will receive targeted prophylaxis (figure 1). The study start date is 24 June 2021, and the estimated study completion date is 30 April 2025.

Study objectives

The primary objective of this study is to compare the frequency and severity of infectious complications between the transperineal and transrectal approaches to prostate biopsy. The secondary objectives of this study include comparing the frequency of infectious complications between approaches within three different subgroups: biopsy-naïve, prior negative biopsies or active surveillance cohorts. Additional objectives include comparison of other adverse events, biopsy-associated pain and anxiety, and cancer detection rates.

Study population

The study population will include men who are recommended to undergo prostate biopsy as part of routine clinical care.

Inclusion criteria

- Age ≥18 years.
- Need for prostate biopsy (first-time biopsy, prior negative biopsy, on active surveillance for existing prostate cancer).

Exclusion criteria

- Acute prostatitis within the last 6 months.

- Current non-urological bacterial infection requiring active treatment with antibiotics.
- Unfit to undergo prostate biopsy under local anaesthesia.
- Prior definitive therapy for prostate cancer, such as radiation therapy or partial gland ablation.
- Men in whom artefact would reduce the quality of prostate MRI (orthopaedic pelvic implants).
- Contraindication to prostate MRI (claustrophobia, pacemaker, chronic kidney disease).

Sample size

We aim to enrol 1700 (n=680 active surveillance, n=620 prior negative biopsy, n=400 first-time biopsy) subjects in this study, with equal randomisation between groups. We assume that the infection rate in the transperineal group is 0.5%. Given a one-sided α of 0.05, 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 ranging from 1% to 5%.[61–68]

Randomisation, blinding and treatment allocation

Study sites will use a two-stage consent process[60] except for those that predominantly perform transperineal biopsies, which will use the traditional one-stage consent. In one-stage consent, which is the traditional approach to RCT consent, patients receive information about research procedures (such as randomisation) and all possible allocated treatments in a single visit. With the two-stage consent, subjects first give consent to research procedures and randomisation and then subsequently give consent to their randomised allocation.[60] Men who sign first-stage consent will be randomised in a 1:1 ratio to receive transperineal biopsy or transrectal biopsy, and those randomised to the transrectal approach will receive transrectal biopsy per protocol. Men randomised to transperineal biopsy will undergo a second consent discussion with the enrolling investigator, where the risks and benefits of transperineal biopsy will be explained, and the decision of whether to undergo the transperineal approach or the standard transrectal approach can then be made. Those who agree to undergo transperineal biopsy will then sign the second-stage consent form. The advantage of the two-stage consent process comes from the fact that only subjects randomised to the transperineal approach will undergo discussion of that intervention, with the goal of reducing the subject's decisional anxiety, confusion and information overload.[60]

Consent will be valid for 8 months to accommodate for biopsy scheduling (online supplemental appendix 1), reducing the number of reconsents and aligning with the standard of care timeline for biopsy procedures.

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 (biopsy-naïve, prior negative biopsy and active surveillance) and implemented by a central web-based Research Electronic Data Capture (REDCap) randomisation model, which prevents an investigator from learning allocation before a patient is unambiguously registered into the study and from changing allocation afterwards, thus ensuring full allocation concealment. Randomisation will be performed by a study coordinator via REDCap during the enrollment process. After a subject has been allocated, the group assignment will become permanently locked and unmodifiable. Allocation assignments will then be unblinded to subjects, providers, study coordinators and data analysts.

Intervention

For patients undergoing transrectal biopsy, a rectal culture will be performed to screen for fluoroquinolone-resistant organisms, and targeted antibiotic prophylaxis will be administered in accordance with AUA guidelines.[20] In culture-negative subjects, a fluoroquinolone will be administered. In culture-positive subjects, the fluoroquinolone regimen may be exchanged with an alternative antibiotic or augmented with a second antibiotic; the exact regimens used will vary per patient and site based on local antibiogram data. No antibiotic prophylaxis will be administered for patients undergoing transperineal biopsy.

Study investigators will follow a standardised biopsy technique described by Kubo *et al* to administer lidocaine during transperineal biopsy.[53] At each study site, the choice of commercial MRI-targeted biopsy platform is left to the provider's discretion.

In both arms of the study, the number of systematic biopsy cores will be standardised to 12 cores, and the number of targeted cores will be standardised to 3 cores per target, with a maximum of 3 regions of interest to be chosen for targeted biopsy. The technique for transrectal prostate biopsy is performed as described by Kasivisvanathan *et al*.[69] The technique for transperineal prostate biopsy is performed as described by Urkmez *et al*.[70]

Technical deviations that may occur during routine clinical care will be recorded for each case, monitored by the Weill Cornell Medicine (WCM) Data Safety Monitoring Committee and compared between groups. Research coordinators at each site will randomly select three transperineal and three transrectal biopsy videos uploaded every 3 months. Investigators will review and discuss during quarterly video conferences to ensure consistent procedural fidelity throughout the study.

Outcomes to be measured

Patients will be followed for approximately 7 (7±2) days following biopsy to evaluate for adverse events. Subjects experiencing an adverse event beyond 7 days will be followed until resolution or stabilisation. A cut-off of 7 days was chosen because the vast majority of postbiopsy infections will occur within this time frame.[71 72] In addition, evaluation at 7 days has been previously used and

Table 1 Trial Definitions of Infectious Complications

Infectious complications	Criteria
Uncomplicated UTI	1. Symptoms of dysuria, urgency, frequency, or hematuria 2. Pyuria* and/or bacteriuria† 3. No fever
Complicated UTI	1. Symptoms of fever, flank pain, nausea/vomiting 2. Pyuria and/or bacteriuria
Urosepsis	1. Meets criteria for sepsis, severe sepsis, or septic shock[81 82] 2. Evidence of urinary pathogen growth in urine or blood cultures

*Pyruia is defined as >5 white blood cells per high-powered field or positive leucocyte esterase on urine dipstick
†Bacteriuria is defined as ≥105 colony-forming units (cfu)/mL or <105 cfu/mL in high-risk patients.[83]
UTI, urinary tract infection.

is sufficiently long enough to capture non-infectious adverse events.[73]

Adverse events

The primary objective of this trial is to compare the frequency and severity of infectious complications experienced by patients undergoing transperineal biopsy versus transrectal biopsy. Secondary outcomes include non-infectious adverse events, such haematuria or urinary retention. Patients will be assessed for complications by way of questionnaire administered 5–9 days postbiopsy. Patients indicating that they have experienced an adverse event will be contacted by the study team to seek further details. In addition, all relevant medical records will be requested. Prospective review of medical records will capture microbiological outcomes, including fluoroquinolone resistance rates in prebiopsy rectal cultures as well as urine/blood culture results—bacterial growth and associated resistance patterns—in patients who develop a postbiopsy infection. Adverse events will be classified in accordance with Common Terminology Criteria for Adverse Events V.5.0.

The criteria for infectious complications are listed in table 1.

Pain, anxiety and discomfort

A questionnaire will be given to patients immediately after the biopsy and at 5–9 days postbiopsy (online supplemental appendix 2–4). The questionnaire captures discomfort, pain, fear/anxiety using a Numerical Rating Scale (0–10), with higher scores indicating a greater intensity of symptoms.

Biopsy pathology

The proportion of men diagnosed with low grade (grade group (GG) 1) and non-low-grade (GG≥2) prostate cancer will be compared by biopsy approach from final pathology review. 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 millimetre), and total number of negative cores. To compare outcomes, prostate cancer grade will be categorised into low grade or non-low grade.[34]

Statistical analyses

Analysis of infection, detection of non-low-grade cancer, overdetection of low-grade cancer, grade 1 complications (patient-reported haematuria, haematospermia or haematochezia) and presence versus absence of other biopsy-related complications grade 2 or above will be performed by logistic regression with site and biopsy-naïve versus prior negative biopsy versus active surveillance as fixed effect covariates. Absolute risk differences will be calculated by applying the OR 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 GG≥2 cancer up to 2 years after randomisation (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 vary by race (African American vs not) or diagnostic setting (biopsy-naïve vs prior negative vs active surveillance) by adding those variables and the associated interaction terms in separate logistic regression models.

Rates of missing data are expected to be low as all outcomes will be assessed within a short period of time after biopsy. Hence, we do not anticipate the need for statistical methods to handle missing data. However, if rates of missing data are >5%, we will implement multiple imputation using chained equations.

To compare the detection of non-low-grade cancer on biopsy with systematic versus MRI-targeted biopsy stratified by transperineal versus transrectal approaches, the analyses will be conducted separately for the prior negative biopsy and active surveillance cohorts. For the prior negative biopsy cohort, we will create a model with the outcome of non-low-grade cancer using predictors from the standard Prostate Biopsy Collaborative Group model in addition to Prostate Imaging-Reporting and Data System (PI-RADS) V.2 MRI score and prostate volume.[74] For the active surveillance cohort, we will use a similar

approach but use the Canary 'base' model for biopsy outcome.[75] We will report the increase in discrimination associated with using MRI volume and PI-RADS score and conduct decision curve analysis, a decision-analytical technique that weights the value of avoiding unnecessary biopsy compared with missing high-grade cancer, to assess the clinical utility of these models.[76]

Ethics and dissemination

The Institutional Review Board of the Biomedical Research Alliance of New York (BRANY) approved the research protocol (protocol number #18-02-365, approved 20 April 2020). Amendments to the study protocol will be submitted to the BRANY for approval and disseminated to all study sites. Eligible patients will be informed of the study by participating urologists 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 necessary to consider study participation. Patients choosing to participate in the study will be consented by trial coordinators within the privacy of a clinical exam room. Study staff will explain the research objectives, risks and benefits of study participation, and subject rights and responsibilities to each potential subject. Electronic consent will also be available to patients who are scheduled for biopsy via phone following a clinic appointment and/or MRI. Eligible patients will be contacted by a study team member (ie, 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 electronic medical record message.

Study data will be prospectively collected from patient medical records and patient surveys. In all participating centres, the site-specific research coordinator will perform baseline data acquisition and medical record abstraction. These data will be entered into standardised clinical report forms housed within REDCap hosted at WCM. The WCM research coordinator will be the only study team member with the ability to review deidentified data across sites in order to conduct data quality checks and share information with the study biostatistician. To ensure accuracy of data entered in the REDCap database from source documents (including surveys and medical record abstraction), sites will perform 100% visual review and conduct double data entry for a sample (ie, 10%) of the data. Data quality checks will be conducted every 6 months, coinciding with data safety and monitoring committee (DSMC) reviews.

For protocol deviations meeting immediately reportable criteria, the primary concern of the DSMC 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, which operates independently from trial sponsors and investigators, decides that the reported protocol deviation impacts any of the above factors, it may recommend modifications, suspension or termination of the study. Interim study findings will be communicated if modifications are recommended. The DSMC will require the primary investigator to submit confirmation to the DSMC that the modification(s) have been made, or to submit a reason why the investigator did not agree with the DSMC's recommendation. The trial results will be shared in peer-reviewed medical journals and scientific conferences.

Patient and public involvement

Patients and/or the public were not involved in the design, conduct or reporting of this research.

DISCUSSION

Our multicentre study used a pragmatic clinical trial design type to evaluate the safety and efficacy of the transperineal prostate biopsy approach relative to the transrectal biopsy approach. While an explanatory trial design may ascertain whether an intervention is effective in carefully controlled conditions—a narrowly defined population, a limited number of expert clinicians—a pragmatic trial aims to have greater applicability to the settings more typical of the patients who receive care and where they receive it.[77] Among pragmatic trials, other designs such as registry-based and cluster-randomised trials offer different approaches to examining certain clinical questions, but these trial designs may not offer the best strategy in determining the optimal prostate biopsy approach.

Given the high costs associated with structuring a multicentre RCT, registry-based clinical trials offer researchers a low-cost method to evaluate clinical interventions at a large scale that still benefits from the prospective nature of an RCT.[78] Such a methodology was not considered for the current trial because of the key importance of patient-reported outcomes of adverse events, which are not typically captured in registry-based trials. Another approach for pragmatic trials is to use cluster randomisation, where the clinician rather than the patient is randomised. This design is used to compare approaches that are widely implemented in the community such that it would be appropriate for a clinician to offer in routine care. Take, for instance, a cluster randomised trial of two different approaches to the lymph node dissection in radical prostatectomy.[79] Cluster randomised trials are therefore not appropriate for testing experimental interventions. At the time of protocol development, transperineal biopsy was generally considered experimental, was not widely used in routine practice and was therefore not appropriate for a cluster randomised trial.

Similar considerations apply for the Rethinking Clinical Trials (REaCT) framework. For instance, Hilton *et al* used the eight steps of the REaCT process to analyse two standard-of-care interventions for primary prophylaxis of febrile neutropenia in patients with breast cancer

on chemotherapy.[80] As transperineal biopsy could not be considered standard-of-care at the time of protocol development, it would have been inappropriate to adopt the complete REaCT approach. Nonetheless, our trial design mirrors several key elements: selection of clinically relevant and practical questions, appropriate study design and well-defined end points, and real-time data capture using electronic medical records. As such, our current approach offers the best method for answering the question of whether the transperineal prostate biopsy approach is superior to the transrectal biopsy approach.

Author affiliations
[1]Department of Urology, NewYork-Presbyterian Weill Cornell Medical Center, New York, New York, USA
[2]Department of Urology, Memorial Sloan Kettering Cancer Center, New York, New York, USA
[3]Brady Urological Institute, Johns Hopkins School of Medicine, Baltimore, Maryland, USA
[4]Department of Urology, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA
[5]Einstein Urology, Albert Einstein Healthcare Network, Philadelphia, Pennsylvania, USA
[6]Department of Urology, University of Michigan Medical School, Ann Arbor, Michigan, USA
[7]Department of Surgery, Division of Urology, University of Connecticut School of Medicine, Farmington, Connecticut, USA
[8]Department of Surgical Oncology, Division of Urology, Fox Chase Cancer Center, Philadelphia, Pennsylvania, USA
[9]Department of Urology, Case Western Reserve University School of Medicine, Cleveland, Ohio, USA
[10]Department of Urology, MedStar Georgetown University Hospital, Washington, District of Columbia, USA

Contributors JH, AV and EMS made substantial contributions to the conception or design of the work. AZ, MEA, BE, AS, CP, AER, DAG, GW, SG, JSM, AG, JNG, BTR, AC, JES, KJK and TRZ made significant contributions to the acquisition or analysis of the data for the work. JH, AZ, AV, TRZ and EMS contributed to the drafting of the manuscript. MEA, BE, AS, CP, AER, DAG, GW, SG, JSM, AG, JG, BTR, AC, JES and KJK contributed to the critical revision of the manuscript for intellectual content. All authors approve the final version of the manuscript to be published. All authors agree to be accountable for all aspects of the work.

Funding This work was funded by grants from the National Institutes of Health R01 CA241758 and Patient-Centered Outcomes Research Institute CER-2019C2-17372.

Disclaimer Study sponsors were not involved in the study design, data collection, data management, analysis, or interpretation of the data, and they do not have final authority over these activities.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD
Alec Zhu http://orcid.org/0000-0003-1935-483X

REFERENCES

1 Loeb S, Carter HB, Berndt SI, *et al*. Complications after prostate biopsy: data from SEER-Medicare. *J Urol* 2011;186:1830–4.
2 Welch HG, Fisher ES, Gottlieb DJ, *et al*. Detection of prostate cancer via biopsy in the medicare-SEER population during the PSA era. *J Natl Cancer Inst* 2007;99:1395–400.
3 Cooperberg MR, Carroll PR. Trends in management for patients with localized prostate cancer, 1990-2013. *JAMA* 2015;314:80.
4 Litwin MS, Tan HJ. The diagnosis and treatment of prostate cancer: a review. *JAMA* 2017;317:2532–42.
5 Williamson DA, Barrett LK, Rogers BA, *et al*. Infectious complications following transrectal ultrasound-guided prostate biopsy: new challenges in the era of multidrug-resistant Escherichia coli. *Clin Infect Dis* 2013;57:267–74.
6 Lindert KA, Kabalin JN, Terris MK. Bacteremia and bacteriuria after transrectal ultrasound guided prostate biopsy. *J Urol* 2000;164:76–80.
7 Borghesi M, Ahmed H, Nam R, *et al*. Complications after systematic, random, and image-guided prostate biopsy. *Eur Urol* 2017;71:353–65.
8 Grossman DC, Curry SJ, Owens DK, *et al*. Screening for prostate cancer: US preventive services Task force recommendation statement. *JAMA* 2018;319:1901–13.
9 Mosharafa AA, Torky MH, El Said WM, *et al*. Rising incidence of acute prostatitis following prostate biopsy: fluoroquinolone resistance and exposure is a significant risk factor. *Urology* 2011;78:511–4.
10 Nam RK, Saskin R, Lee Y, *et al*. Increasing hospital admission rates for urological complications after transrectal ultrasound guided prostate biopsy. *J Urol* 2013;189(1 Suppl):S12–7.
11 Womble PR, Dixon MW, Linsell SM, *et al*. Infection related hospitalizations after prostate biopsy in a statewide quality improvement collaborative. *J Urol* 2014;191:1787–92.
12 Minamida S, Satoh T, Tabata K, *et al*. Prevalence of fluoroquinolone-resistant Escherichia coli before and incidence of acute bacterial prostatitis after prostate biopsy. *Urology* 2011;78:1235–9.
13 Carlson WH, Bell DG, Lawen JG, *et al*. Multi-drug resistant E.coli urosepsis in physicians following transrectal ultrasound guided prostate biopsies--three cases including one death. *Can J Urol* 2010;17:5135–7.
14 Toren P, Razik R, Trachtenberg J. Catastrophic sepsis and hemorrhage following transrectal ultrasound guided prostate biopsies. Can Urol Assoc J 2010;4:12.
15 Al-Otaibi MF, Al-Taweel W, Bin-Saleh S, *et al*. Disseminated intravascular coagulation following transrectal ultrasound guided prostate biopsy. *J Urol* 2004;171:346.
16 Borer A, Gilad J, Sikuler E, *et al*. Fatal Clostridium sordellii ischio-rectal abscess with septicaemia complicating ultrasound-guided transrectal prostate biopsy. J Infect 1999;38:128–9.
17 Erdogan H, Ekinci MN, Hoscan MB, *et al*. Acute bacterial meningitis after transrectal needle biopsy of the prostate: a case report. *Prostate Cancer Prostatic Dis* 2008;11:207–8.
18 Bell N, Connor Gorber S, Shane A, *et al*. Recommendations on screening for prostate cancer with the prostate-specific antigen test. *CMAJ* 2014;186:1225–34.
19 Jiang P, Liss MA, Szabo RJ. Targeted antimicrobial prophylaxis does not always prevent sepsis after transrectal prostate biopsy. *J Urol* 2018;200:361–8.
20 Liss MA, Ehdaie B, Loeb S, *et al*. An update of the American urological association white paper on the prevention and treatment of the more common complications related to prostate biopsy. *J Urol* 2017;198:329–34.
21 Hadjipavlou M, Eragat M, Kenny C, *et al*. Effect of augmented antimicrobial prophylaxis and rectal swab culture-guided targeted prophylaxis on the risk of sepsis following transrectal prostate biopsy. *Eur Urol Focus* 2020;6:95–101.
22 Cussans A, Somani BK, Basarab A, *et al*. The role of targeted prophylactic antimicrobial therapy before transrectal ultrasonography-guided prostate biopsy in reducing infection rates: a systematic review. *BJU Int* 2016;117:725–31.
23 Pilatz A, Dimitropoulos K, Veeratterapillay R, *et al*. Antibiotic prophylaxis for the prevention of infectious complications following

prostate biopsy: a systematic review and meta-analysis. *J Urol* 2020;204:224–30.
24 Newman TH, Stroman L, Hadjipavlou M, *et al*. Exit from transrectal prostate biopsies (TREXIT): sepsis rates of transrectal biopsy with rectal swab culture guided antimicrobials versus freehand transperineal biopsy. *Prostate Cancer Prostatic Dis* 2022;25:283–7.
25 Tops SCM, Grootenhuis JGA, Derksen AM, *et al*. The effect of different types of prostate biopsy techniques on post-biopsy infectious complications. *J Urol* 2022;208:109–18.
26 Xiang J, Yan H, Li J, *et al*. Transperineal versus transrectal prostate biopsy in the diagnosis of prostate cancer: a systematic review and meta-analysis. *World J Surg Oncol* 2019;17:31.
27 Basourakos SP, Alshak MN, Lewicki PJ, *et al*. Role of prophylactic antibiotics in transperineal prostate biopsy: a systematic review and meta-analysis. *Eur Urol Open Sci* 2022;37:53–63.
28 Jacewicz M, Günzel K, Rud E, *et al*. Antibiotic prophylaxis versus no antibiotic prophylaxis in transperineal prostate biopsies (NORAPP): a randomised, open-label, non-inferiority trial. *Lancet Infect* Dis 2022;22:1465–71.
29 Castellani D, Pirola GM, Law YXT, *et al*. Infection rate after transperineal prostate biopsy with and without prophylactic antibiotics: results from a systematic review and meta-analysis of comparative studies. *J* Urol 2022;207:25–34.
30 Venkatesan AM, Kundu S, Sacks D, *et al*. Practice guidelines for adult antibiotic prophylaxis during vascular and interventional radiology procedures. written by the Standards of practice Committee for the Society of interventional radiology and endorsed by the cardiovascular interventional radiological Society of Europe and Canadian interventional radiology association [corrected]. *J Vasc Interv Radiol* 2010;21:1611–30.
31 Pilatz A, Veeratterapillay R, Dimitropoulos K, *et al*. European association of urology position paper on the prevention of infectious complications following prostate biopsy. *Eur Urol* 2021;79:11–5.
32 Meyer AR, Mamawala M, Winoker JS, *et al*. Transperineal prostate biopsy improves the detection of clinically significant prostate cancer among men on active surveillance. *J Urol* 2021;205:1069–74.
33 Chang DTS, Challacombe B, Lawrentschuk N. Transperineal biopsy of the prostate -- is this the future? *Nat Rev Urol* 2013;10:690–702.
34 Kasivisvanathan V, Dufour R, Moore CM, *et al*. Transperineal magnetic resonance image targeted prostate biopsy versus transperineal template prostate biopsy in the detection of clinically significant prostate cancer. *J Urol* 2013;189:860–6.
35 Radtke JP, Kuru TH, Boxler S, *et al*. Comparative analysis of transperineal template saturation prostate biopsy versus magnetic resonance imaging targeted biopsy with magnetic resonance imaging-ultrasound fusion guidance. *J Urol* 2015;193:87–94.
36 Huang H, Wang W, Lin T, *et al*. Comparison of the complications of traditional 12 cores transrectal prostate biopsy with image fusion guided transperineal prostate biopsy. *BMC Urol* 2016;16:68.
37 Hansen NL, Kesch C, Barrett T, *et al*. Multicentre evaluation of targeted and systematic biopsies using magnetic resonance and ultrasound image-fusion guided transperineal prostate biopsy in patients with a previous negative biopsy. *BJU Int* 2017;120:631–8.
38 Siddiqui MM, Rais-Bahrami S, Turkbey B, *et al*. Comparison of mr/ultrasound fusion-guided biopsy with ultrasound-guided biopsy for the diagnosis of prostate cancer. *JAMA* 2015;313:390–7.
39 Pokorny MR, de Rooij M, Duncan E, *et al*. Prospective study of diagnostic accuracy comparing prostate cancer detection by transrectal ultrasound-guided biopsy versus magnetic resonance (Mr) imaging with subsequent MR-guided biopsy in men without previous prostate biopsies. *Eur Urol* 2014;66:22–9.
40 Quentin M, Blondin D, Arsov C, *et al*. Prospective evaluation of magnetic resonance imaging guided in-bore prostate biopsy versus systematic transrectal ultrasound guided prostate biopsy in biopsy naïve men with elevated prostate specific antigen. *J Urol* 2014;192:1374–9.
41 Arsov C, Rabenalt R, Blondin D, *et al*. Prospective randomized trial comparing magnetic resonance imaging (MRI) -guided in-bore biopsy to MRI-ultrasound fusion and transrectal ultrasound-guided prostate biopsy in patients with prior negative biopsies. *Eur Urol* 2015;68:713–20.
42 Sonn GA, Margolis DJ, Marks LS. Target detection: magnetic resonance imaging-ultrasound fusion–guided prostate biopsy. *Urologic Oncology: Seminars and Original Investigations* 2014;32:903–11.
43 Filson CP, Natarajan S, Margolis DJA, *et al*. Prostate cancer detection with magnetic resonance-ultrasound fusion biopsy: the role of systematic and targeted biopsies. *Cancer* 2016;122:884–92.
44 Liu W, Patil D, Howard DH, *et al*. Impact of prebiopsy magnetic resonance imaging of the prostate on cancer detection and treatment patterns. *Urol Oncol* 2019;37:181.
45 Rosenkrantz AB, Hemingway J, Hughes DR, *et al*. Evolving use of prebiopsy prostate magnetic resonance imaging in the Medicare population. *J Urol* 2018;200:89–94.
46 Kasivisvanathan V, Rannikko AS, Borghi M, *et al*. MRI-targeted or standard biopsy for prostate-cancer diagnosis. *N Engl J Med* 2018;378:1767–77.
47 Vickers AJ. Effects of magnetic resonance imaging targeting on overdiagnosis and overtreatment of prostate cancer. *Eur Urol* 2021;80:567–72.
48 Bjurlin MA, Carroll PR, Eggener S, *et al*. Update of the standard operating procedure on the use of multiparametric magnetic resonance imaging for the diagnosis, staging and management of prostate cancer. *J Urol* 2020;203:706–12.
49 Mottet N, van den Bergh RCN, Briers E, *et al*. EAU-eanm-estro-esur-siog guidelines on prostate cancer-2020 update. Part 1: screening, diagnosis, and local treatment with curative intent. *Eur Urol* 2021;79:243–62.
50 Rai BP, Mayerhofer C, Somani BK, *et al*. Magnetic resonance imaging/ultrasound fusion-guided transperineal versus magnetic resonance imaging/ultrasound fusion-guided transrectal prostate biopsy-a systematic review. *Eur Urol Oncol* 2021;4:904–13.
51 Halpern JA, Sedrakyan A, Dinerman B, *et al*. Indications, utilization and complications following prostate biopsy: new York state analysis. *J* Urol 2017;197:1020–5.
52 Tamhankar AS, El-Taji O, Vasdev N, *et al*. The clinical and financial implications of a decade of prostate biopsies in the NHS: analysis of hospital episode statistics data 2008-2019. *BJU Int* 2020;126:133–41.
53 Kubo Y, Kawakami S, Numao N, *et al*. Simple and effective local anesthesia for transperineal extended prostate biopsy: application to three-dimensional 26-core biopsy. *Int J Urol* 2009;16:420–3.
54 Meyer AR, Joice GA, Schwen ZR, *et al*. Initial experience performing in-office ultrasound-guided transperineal prostate biopsy under local anesthesia using the precisionpoint transperineal access system. *Urology* 2018;115:8–13.
55 Marra G, Zhuang J, Marquis A, *et al*. Pain in men undergoing transperineal free-hand multiparametric magnetic resonance imaging fusion targeted biopsies under local anesthesia: outcomes and predictors from a multicenter study of 1,008 patients. *J* Urol 2020;204:1209–15.
56 McCulloch P, Taylor I, Sasako M, *et al*. Randomised trials in surgery: problems and possible solutions. *BMJ* 2002;324:1448–51.
57 Djurisic S, Rath A, Gaber S, *et al*. Barriers to the conduct of randomised clinical trials within all disease areas. *Trials* 2017;18.
58 Solomon MJ, McLeod RS. Should we be performing more randomized controlled trials evaluating surgical operations? *Surgery* 1995;118:459–67.
59 Vickers AJ, Vertosick EA, Carlsson SV, *et al*. Patient accrual and understanding of informed consent in a two-stage consent design. *Clin Trials* 2021;18:377–82.
60 Vickers AJ, Young-Afat DA, Ehdaie B, *et al*. Just-in-time consent: the ethical case for an alternative to traditional informed consent in randomized trials comparing an experimental intervention with usual care. *Clin Trials* 2018;15:3–8.
61 Rosario DJ, Lane JA, Metcalfe C, *et al*. Short term outcomes of prostate biopsy in men tested for cancer by prostate specific antigen: prospective evaluation within protect study. *BMJ* 2012;344:d7894.
62 Lundström K-J, Drevin L, Carlsson S, *et al*. Nationwide population based study of infections after transrectal ultrasound guided prostate biopsy. *J Urol* 2014;192:1116–22.
63 Bruyère F, Malavaud S, Bertrand P, *et al*. Prosbiotate: a multicenter, prospective analysis of infectious complications after prostate biopsy. *J* Urol 2015;193:145–50.
64 Wagenlehner FME, van Oostrum E, Tenke P, *et al*. Infective complications after prostate biopsy: outcome of the global prevalence study of infections in urology (GPIU) 2010 and 2011, a prospective multinational multicentre prostate biopsy study. *Eur* Urol 2013;63:521–7.
65 Loeb S, van den Heuvel S, Zhu X, *et al*. Infectious complications and hospital admissions after prostate biopsy in a European randomized trial. *Eur* Urol 2012;61:1110–4.
66 Unnikrishnan R, El-Shafei A, Klein EA, *et al*. For single dosing, levofloxacin is superior to ciprofloxacin when combined with an aminoglycoside in preventing severe infections after prostate biopsy. *Urology* 2015;85:1241–6.
67 Abughosh Z, Margolick J, Goldenberg SL, *et al*. A prospective randomized trial of povidone-iodine prophylactic cleansing of the rectum before transrectal ultrasound guided prostate biopsy. *J Urol* 2013;189:1326–31.

68 Park DS, Hwang JH, Choi DK, *et al*. Control of infective complications of transrectal prostate biopsy. *Surg Infect (Larchmt)* 2014;15:431–6.
69 Kasivisvanathan V, Jichi F, Klotz L, *et al*. A multicentre randomised controlled trial assessing whether MRI-targeted biopsy is non-inferior to standard transrectal ultrasound guided biopsy for the diagnosis of clinically significant prostate cancer in men without prior biopsy: a study protocol. *BMJ Open* 2017;7:e017863.
70 Urkmez A, Demirel C, Altok M, *et al*. Freehand versus GRID-based transperineal prostate biopsy: a comparison of anatomical region yield and complications. *J Urol* 2021;206:894–902.
71 Forsvall A, Jönsson H, Wagenius M, *et al*. Rate and characteristics of infection after transrectal prostate biopsy: a retrospective observational study. *Scand J Urol* 2021;55:317–23.
72 Danielsen L, Faizi G, Snitgaard S, *et al*. Infections after transrectal ultrasonic guided prostate biopsies-a retrospective study. *Scand J Urol* 2019;53:97–101.
73 Ghani KR, Dundas D, Patel U. Bleeding after transrectal ultrasonography-guided prostate biopsy: a study of 7-day morbidity after a six-, eight- and 12-core biopsy protocol. *BJU Int* 2004;94:1014–20.
74 Ankerst DP, Straubinger J, Selig K, *et al*. A contemporary prostate biopsy risk calculator based on multiple heterogeneous cohorts. *Eur Urol* 2018;74:197–203.
75 Lin DW, Newcomb LF, Brown MD, *et al*. Evaluating the four kallikrein panel of the 4kscore for prediction of high-grade prostate cancer in men in the Canary prostate active surveillance study. *Eur Urol* 2017;72:448–54.
76 Vickers AJ, Elkin EB. Decision curve analysis: a novel method for evaluating prediction models. *Med Decis Making* 2006;26:565–74.
77 Sedgwick P. Explanatory trials versus pragmatic trials. *BMJ* 2014;349(nov13 3):g6694.
78 James S, Rao SV, Granger CB. Registry-Based randomized clinical trials -- a new clinical trial paradigm. *Nat Rev Cardiol* 2015;12:312–6.
79 Touijer KA, Sjoberg DD, Benfante N, *et al*. Limited versus extended pelvic lymph node dissection for prostate cancer: a randomized clinical trial. *Eur Urol Oncol* 2021;4:532–9.
80 Hilton J, Mazzarello S, Fergusson D, *et al*. Novel methodology for comparing standard-of-care interventions in patients with cancer. *J Oncol Pract* 2016;12:e1016–24.
81 Singer M, Deutschman CS, Seymour CW, *et al*. The third International consensus definitions for sepsis and septic shock (sepsis-3). *JAMA* 2016;315:801.
82 Zembower TR, Maxwell KM, Nadler RB, *et al*. Evaluation of targeted antimicrobial prophylaxis for transrectal ultrasound guided prostate biopsy: a prospective cohort trial. *BMC Infect Dis* 2017;17:401.
83 Miller JM, Binnicker MJ, Campbell S, *et al*. A guide to utilization of the microbiology laboratory for diagnosis of infectious diseases: 2018 update by the infectious diseases Society of America and the American Society for microbiology. *Clin Infect Dis* 2018;67:813–6.

Appendix 1.

	Month -8 to Day 0	Day 0	Day 5 to 9
Eligibility	X[1]		
Informed consent	X		
Demographics	X		
Medical history[2]	X		
Physical exam[3]	X		
Randomization	X		
PSA	X		
Rectal swab[4]	X		
Prostate biopsy		X	
Assessment of Adverse Events[5]			X
Concomitant Medications[6]		X	X

[1]To be performed prior to informed consent.
[2]Medical comorbidities, indication for biopsy, multiparametric MRI findings, and history of prior biopsy or infection.
[3]Height and weight.
[4]Performed for transrectal biopsy only.
[5]Assessed by patient questionnaire. Events will be grading using Common Terminology Criteria for Adverse Events (CTCAE) v5.0.
[6]Assessed by patient questionnaires.

Appendix 2.

Timing for assessment of study variables

Assessment	Baseline pre-biopsy	Day of biopsy	7-days post-biopsy
Baseline history and physical exam, screening, consent	X		
Prior Biopsy (Yes/No)	X		
Prior Biopsy infection (Yes/No)	X		
PSA	X		
Indication for Biopsy	X		
Multiparametric MRI findings	X		
Randomization: transperineal vs. transrectal biopsy	X		
infection risk determination for transrectal biopsy prophylaxis	X		
Biopsy completed (Yes/No)		X	
Biopsy duration (minutes)		X	
Pain (Visual Analogue Scale)		X	X
Discomfort (Visual Analogue Scale)		X	X
Anxiety (Likert 5 levels)		X	
Decision regret			X
Adverse events (Yes/No) and Bother			X
Urinary Tract Infection			X
Sepsis			X
Urinary retention			X
Fever			X
Hematuria			X
Hematochezia			X
Hematospermia			X
Urinary Tract Infection diagnosed by Health Care Proxy			X
Unplanned Health Care Proxy contact			X
Qualitative responses			X
Biopsy pathologic outcomes, if cancer:			X
Gleason grade group(s)			X
Number of cores positive			X
Number of cores negative			X
Maximum cancer core length			X
Targeted Biopsy positive (Yes/No/Not Applicable)			X
Systematic Biopsy positive (Yes/No)			X
Location of positive cores			X

Appendix 3.

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 assistant.

Appendix 4.

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.