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

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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

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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,

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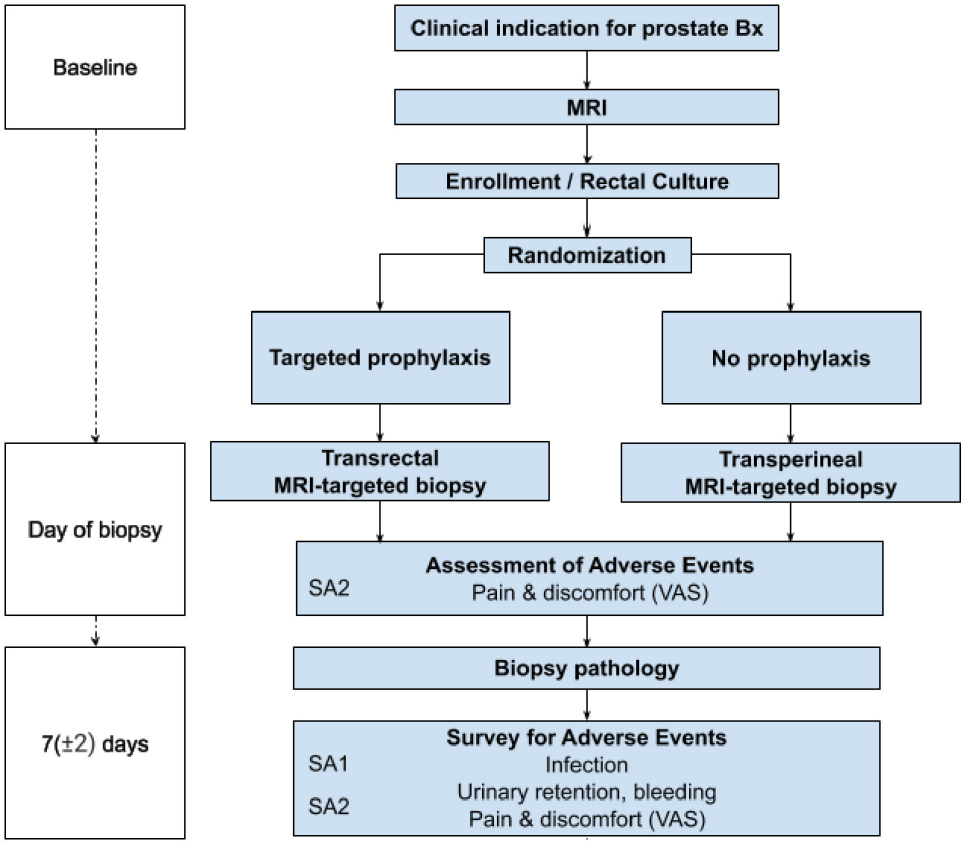

Figure 1 Consolidated Standards of Reporting Trials (CONSORT) diagram.

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.

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- 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

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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

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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

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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.

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