

BMJ Open Comparing biparametric to multiparametric MRI in the diagnosis of clinically significant prostate cancer in biopsy-naïve men (PRIME): a prospective, international, multicentre, non-inferiority within-patient, diagnostic yield trial protocol

Aqua Asif ¹, Arjun Nathan ^{1,2}, Alexander Ng,¹ Pramit Khetrapal,^{1,3} Vinson Wai-Shun Chan,¹ Francesco Giganti,^{1,4} Clare Allen,^{1,4} Alex Freeman,⁵ Shonit Punwani,^{4,6} Paula Lorgelly,^{7,8} Caroline S Clarke ⁹, Chris Brew-Graves,¹⁰ Nicola Muirhead,¹⁰ Mark Emberton ^{1,11}, Ridhi Agarwal ^{12,13}, Yemisi Takwoingi,^{12,13} Jonathan J Deeks,^{12,13} Caroline M Moore ^{1,11}, Veeru Kasivisvanathan ^{1,11}, PRIME Trial Group

To cite: Asif A, Nathan A, Ng A, *et al.* Comparing biparametric to multiparametric MRI in the diagnosis of clinically significant prostate cancer in biopsy-naïve men (PRIME): a prospective, international, multicentre, non-inferiority within-patient, diagnostic yield trial protocol. *BMJ Open* 2023;**13**:e070280. doi:10.1136/bmjopen-2022-070280

► 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-2022-070280>).

AA and AN are joint first authors.

Received 19 November 2022
Accepted 10 February 2023



© Author(s) (or their employer(s)) 2023. Re-use permitted under CC BY. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to

Veeru Kasivisvanathan;
veeru.kasi@ucl.ac.uk

ABSTRACT

Introduction Prostate MRI is a well-established tool for the diagnostic work-up for men with suspected prostate cancer (PCa). Current recommendations advocate the use of multiparametric MRI (mpMRI), which is composed of three sequences: T2-weighted sequence (T2W), diffusion-weighted sequence (DWI) and dynamic contrast-enhanced sequence (DCE). Prior studies suggest that a biparametric MRI (bpMRI) approach, omitting the DCE sequences, may not compromise clinically significant cancer detection, though there are limitations to these studies, and it is not known how this may affect treatment eligibility. A bpMRI approach will reduce scanning time, may be more cost-effective and, at a population level, will allow more men to gain access to an MRI than an mpMRI approach.

Methods Prostate Imaging Using MRI±Contrast Enhancement (PRIME) is a prospective, international, multicentre, within-patient diagnostic yield trial assessing whether bpMRI is non-inferior to mpMRI in the diagnosis of clinically significant PCa. Patients will undergo the full mpMRI scan. Radiologists will be blinded to the DCE and will initially report the MRI using only the bpMRI (T2W and DWI) sequences. They will then be unblinded to the DCE sequence and will then re-report the MRI using the mpMRI sequences (T2W, DWI and DCE). Men with suspicious lesions on either bpMRI or mpMRI will undergo prostate biopsy. The main inclusion criteria are men with suspected PCa, with a serum PSA of ≤20 ng/mL and without prior prostate biopsy. The primary outcome is the proportion of men with clinically significant PCa detected (Gleason score ≥3+4 or Gleason grade group

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Prostate Imaging Using MRI±Contrast Enhancement (PRIME) is a pragmatic, prospective, international, multicentre trial being carried out in a range of different healthcare settings.
- ⇒ Its within-patient design allows patients to act as their own control, improving the efficiency and power of the trial compared with a randomised study.
- ⇒ Its within-patient design allows the impact of the dynamic contrast-enhanced sequences (DWIs) on staging decisions and treatment eligibility to be made at an individual patient level.
- ⇒ PRIME will be one of the first trials to carry out quality control in the performance of sites' DWIs prior to their involvement in the trial.
- ⇒ As both biparametric and multiparametric targeted biopsies are carried out in the same patient, it is possible for the performance of one technique to influence the other.

≥2). A sample size of at least 500 patients is required. Key secondary outcomes include the proportion of clinically insignificant PCa detected and treatment decision.

Ethics and dissemination Ethical approval was obtained from the National Research Ethics Committee West Midlands, Nottingham (21/WM/0091). Results of this trial will be disseminated through peer-reviewed publications. Participants and relevant patient support groups will be informed about the results of the trial.

Trial registration number NCT04571840.

INTRODUCTION

This protocol was written according to SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines.¹ MRI is widely established as the gold standard diagnostic imaging modality for detecting clinically significant prostate cancer (PCa).² The landmark PRECISION (Prostate Evaluation for Clinically Important Disease: Sampling Using Image Guidance or Not?) trial established the benefit of detecting clinically significant PCa using MRI and targeting biopsies based on MRI findings.³ The National Prostate Cancer Audit data from England showed that only 62% of patients undergo prostate MRI before biopsy, despite level 1 evidence to support the use of MRI.²⁻⁴

Current recommendations for the use of MRI for detection of PCa focus on the use of multiparametric MRI (mpMRI).^{2,3} mpMRI consists of three sequences: T2-weighted sequence (T2W), diffusion-weighted sequence (DWI) and dynamic contrast-enhanced sequence (DCE). On the DCE sequences, cancer-suspicious areas can demonstrate early wash-in, enhancement and rapid wash-out of contrast.⁵⁻⁸ The DCE sequences involve administering gadolinium contrast via an intravenous cannula. Therefore, it increases scanning time and healthcare costs compared with a biparametric MRI (bpMRI) approach where only T2W and DWI are used. While gadolinium is in widespread use, literature suggests it may accumulate in the basal ganglia, though its clinical relevance is not fully understood.^{9,10} In patients who are likely to get repeated scans over their lifetime, there may be no advantage of using the additional contrast if the bpMRI option is as good as the mpMRI option.

Removing the DCE sequences from the MRI protocol has been suggested as a potential avenue to improve the cost-effectiveness of using MRI in the diagnostic pathway for PCa,^{11,12} and the reduced scanning time required may improve the number of men with suspected PCa accessing an MRI scan. Using bpMRI has demonstrated similar detection rates of PCa as mpMRI, but current evidence is limited primarily to retrospective, single-centre

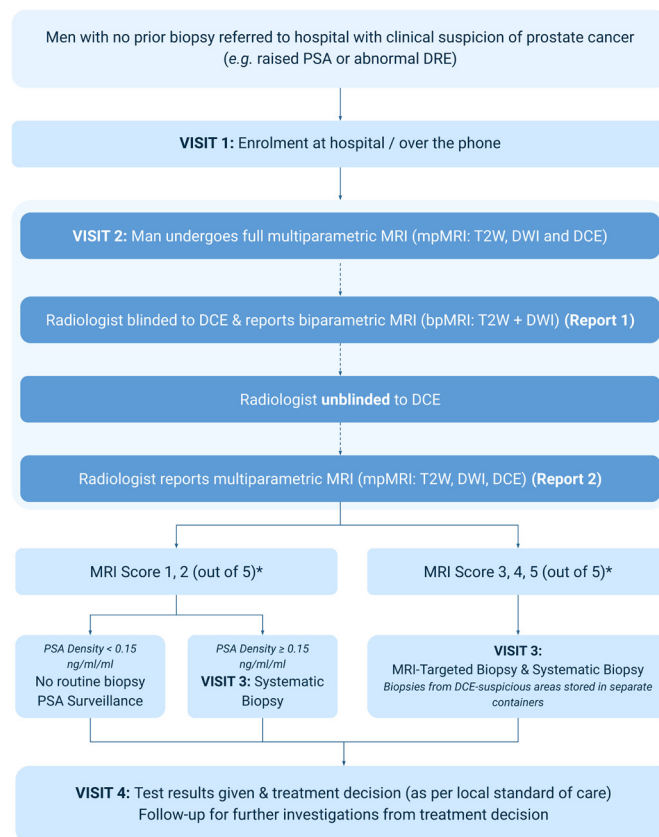


Figure 1 The Prostate Imaging Using MRI±Contrast Enhancement trial schema—the approach prior to MRI. *indicates a 1–5 scale of suspicion for the likelihood that clinically significant PCa is present, with 5 representing the greatest score of suspicion. For MRI to be non-suspicious it needs to be scored 1 or 2 on both Likert and PI-RADS V.2.1 systems. For MRI to be suspicious it can be scored 3, 4 or 5 on either Likert or PI-RADS V.2.1 systems. bpMRI, biparametric MRI; DCE, dynamic contrast-enhanced sequence; DRE, digital rectal examination; DWI, diffusion-weighted sequence; mpMRI, multiparametric MRI; PI-RADS, Prostate Imaging Reporting and Data System; PSA, prostate-specific antigen; T2W, T2-weighted sequence.

studies.^{12,13} The few prospective studies have not been typically robustly designed to evaluate the role of DCE in PCa detection.^{13,14}

The Prostate Imaging Using MRI±Contrast Enhancement (PRIME) trial aims to assess whether bpMRI is non-inferior to mpMRI in the detection of clinically significant PCa. PRIME may redefine the standard of care diagnostic test for men with suspicion of PCa and may allow many more patients who need access to an MRI to get one.

Objectives

The primary objective is to compare the detection of clinically significant PCa (Gleason score ≥3+4 or Gleason grade group ≥2) using bpMRI±targeted biopsy with mpMRI±targeted biopsy.

Key secondary objectives are:

Box 1 Eligibility criteria

- ⇒ Inclusion criteria.
 - Men at least 18 years of age referred with clinical suspicion of PCa.
 - Serum prostate-specific antigen of ≤20 ng/mL.
 - Fit to undergo all procedures listed in the protocol.
 - Able to provide written informed consent.
- ⇒ Exclusion criteria.
 - Prior prostate biopsy.
 - Prior treatment for PCa.
 - Prior prostate MRI on a previous encounter.
 - Contraindication to MRI (eg, claustrophobia, some pacemakers).
 - Contraindication to prostate biopsy.
 - Unfit to undergo any procedures listed in the protocol.

PCa, prostate cancer.

Box 2 Summary of MRI reporting rules

Report 1 (bpMRI: T2W and DWI).

1. The radiologist reporting this will be blinded to DCE, with verification of this via an independent person or an automated system (Medical Image Merge (MIM) by MIM Software Inc.).
2. The radiologist should then interpret the bpMRI sequences *blinded* to DCE.
3. Up to four suspicious areas (score ≥ 3 out of 5 on the Likert or PI-RADS V.2.1 scoring system) can be marked on report 1; if there are more, the four *most suspicious* should only be marked on.
4. The location of the suspicious areas should be labelled according to the PI-RADS V.2.1 41 sector diagram.
5. Once report 1 (bpMRI: T2W and DWI) has been done, this *cannot be altered* after looking at the DCE.

Report 2 (mpMRI: T2W, DWI and DCE).

1. The same radiologist must report both reports 1 and 2.
2. They will then be *unblinded* to the DCE sequence.
3. The radiologist should now complete report 2.
4. The location of the suspicious areas should be similarly labelled according to the PI-RADS V.2.1 41-sector diagram as previously mentioned.
5. On report 2, each of the existing lesions are additionally labelled as one of

bpMRI positive, mpMRI positive.

This occurs when a lesion scores 3, 4 or 5 on both bpMRI and mpMRI based on *either* Likert or PI-RADS V.2.1 scoring systems.

bpMRI positive, mpMRI negative.

This occurs when a lesion scores 3, 4 or 5 on bpMRI on either Likert or PI-RADS V.2.1 scoring systems, but also scores as 1 or 2 on mpMRI on both Likert and PI-RADS V.2.1 scoring systems.

bpMRI negative, mpMRI positive.

There are two instances in which *new targets* may be labelled and drawn onto report 2:

1. *New lesions* scoring 3, 4 or 5, identified by DCE not previously identified on bpMRI should be marked on as new lesions as *DCE targets* and *bpMRI negative, mpMRI positive*.
2. Lesions that appear *larger* on DCE should be treated as two separate targets.
 - One target depicts the completely overlapping segment from report 1 (bpMRI positive, mpMRI positive).
 - The non-overlapping part which would otherwise not be sampled should be labelled as a *new target* (bpMRI negative, mpMRI positive). This is a subjective decision by the radiologist. A typical example of when to declare this as a separate target is if the non-overlapping part enters an adjacent sector on the PI-RADS V.2.1 sector diagram.

A biopsy plan is recommended by the radiologist thereafter for the biopsy operator to follow.

- ▶ To compare the proportion of men who have clinically insignificant PCa (Gleason score 3+3 or Gleason grade group 1) detected for bpMRI versus mpMRI.
- ▶ To compare the proportion of men with non-suspicious MRIs for bpMRI versus mpMRI.
- ▶ To compare the proportion of men with indeterminate scored MRI as reported by bpMRI and mpMRI.

- ▶ To compare the proportion of men with MRIs of adequate standard for reporting for bpMRI versus mpMRI.
- ▶ To compare the diagnostic test performance for bpMRI versus mpMRI.
- ▶ To compare radiological staging for bpMRI versus mpMRI.
- ▶ To compare treatment eligibility decisions for bpMRI when compared with mpMRI.
- ▶ To compare diagnostic performance of bpMRI and mpMRI when using the Likert scoring system in comparison to the Prostate Imaging Reporting and Data System (PI-RADS) V.2.1 scoring system.
- ▶ To compare the cost effectiveness of bpMRI when compared with mpMRI.

Trial design

The PRIME trial is designed as a prospective, multicentre, within-patient, diagnostic yield trial, assessing whether bpMRI is non-inferior to mpMRI for the diagnosis of clinically significant PCa in biopsy-naïve men. A paired cohort design was chosen rather than a randomised trial design for the following reasons:

- ▶ More efficient design (sevenfold lower sample size required) with equivalent quality of evidence in the setting of a diagnostic study.
- ▶ Patients act as their own control due to the within-patient design, thus allowing us to draw conclusions regarding the value of DCE sequences on a per patient level.
- ▶ Allows for the evaluation of the impact of contrast on staging decisions and treatment eligibility decisions at an individual patient level.
- ▶ Patients get the benefit of having targeted biopsies based on the information from both bpMRI and mpMRI information, whereas with a randomised study, patients randomised to one technique will be denied of potential benefit of the other.

METHODS AND ANALYSIS

Trial setting

We expect centres that perform PCa diagnostics and management from the following countries to take part: Argentina, Australia, Belgium, Brazil, Canada, Denmark, France, Finland, Germany, Italy, the Netherlands, Singapore, Spain, UK and USA. Sites will be required to undergo a period of quality control prior to including patients to ensure minimum acceptable standards for the conduct of mpMRI, reporting and targeted biopsy.

Eligibility criteria

Patients will be considered eligible for registration into this trial if they fulfil all of the inclusion criteria and none of the exclusion criteria (box 1).

Interventions

MRI conduct

MRI will be conducted with 1.5 or 3.0 T with pelvic-phased array coils, with or without endorectal coils. The

Table 1 Secondary outcomes in Prostate Imaging Using MRI±Contrast Enhancement

Outcome	Time frame for assessment
Proportion of men with clinically insignificant cancer (Gleason score 3+3/Gleason grade group 1)	When biopsy results are available, at an expected average of 30 days post biopsy
Agreement between bpMRI and mpMRI for score of suspicion	When MRI results are available, at an expected average of 30 days post MRI
Proportion of bpMRI scans and mpMRI whose quality was deemed adequate for reporting	When MRI results are available, at an expected average of 30 days post MRI
Agreement between bpMRI and mpMRI for radiological staging decision	When MRI results are available, at an expected average of 30 days post MRI
Agreement between bpMRI and mpMRI for treatment eligibility	When treatment eligibility is discussed in a multidisciplinary meeting, at an expected average of 30 days post biopsy
Test performance characteristics for bpMRI and mpMRI when using the Likert scoring system in comparison to the PI-RADS scoring system	When biopsy results are available, at an expected average of 30 days post MRI
Proportion of men with clinically significant cancer missed by bpMRI-targeted and mpMRI-targeted biopsies and detected by systematic biopsy	When biopsy results are available, at an expected average of 30 days post biopsy
Cost-effectiveness of bpMRI compared with mpMRI (cost per diagnosis of prostate cancer)	At an expected average of 30 days post intervention

bpMRI, biparametric MRI; mpMRI, multiparametric MRI; PI-RADS, Prostate Imaging Reporting and Data System.

PRECISION study quality control highlighted that the image quality of the DCE sequences was the most variable sequence across sites.³ Therefore, to give DCE a reasonable chance of demonstrating whether it has value, MRI scanner approval for use in the study will be made on the basis of central review of MRI images, using the Prostate Imaging Quality (PI-QUAL) scoring system.¹⁵ In brief, PI-QUAL is a 5-point Likert scoring system, where 1 indicates no sequences are of diagnostic quality and 5 implies that each sequence individually is of optimal diagnostic quality. The objective criteria used to determine PI-QUAL scores are derived from internationally published minimum standards for MRI conduct.¹⁶ If necessary, sites will be given recommendations to improve image quality and will be re-evaluated after optimisation for participation in the study.

Reporting of MRI

Patients will undergo (or will have undergone) standard of care mpMRI as per their local protocol. The radiologists participating in this trial will be blinded to the DCE sequences and will report the MRI using only the biparametric (T2W and DWI) sequences in report 1. After reporting the bpMRI, the same radiologist will be unblinded to the DCE sequences and will re-report the MRI using the mpMRI sequences (T2W, DWI and DCE) in report 2 (figure 1).

The MRIs and lesions are scored on a 1–5 scale of suspicion for the likelihood that clinically significant PCa is present, with 5 representing the greatest score of suspicion. Both the traditional Likert and PI-RADS V.2.1 scoring systems will be used to identify any suspicious lesions in the prostate. Suspicious areas (Likert or

PI-RADS V.2.1 score ≥ 3) on either bpMRI or mpMRI will undergo targeted biopsy of the prostate, with cores from contrast-enhanced suspicious areas stored separately.

A summary of the rules for reporting MRI scans in the PRIME trial is listed in box 2. Please see online supplemental appendix 1 for our model reporting proformas, which radiologists participating in the PRIME trial will use to label lesions.

Non-suspicious bpMRI and mpMRI

Men whose MRIs do not show suspicious areas on bpMRI and mpMRI (ie, scored 1 or 2 on Likert and PI-RADS V.2.1) will be stratified by PSA density. Men with PSA density of <0.15 ng/mL/mL will not undergo biopsy and men with PSA density of ≥ 0.15 ng/mL/mL will undergo systematic biopsy.

Prostate biopsy procedures

MRI-targeted biopsy

Men will undergo MRI-targeted biopsy if either their bpMRI or mpMRI identifies a suspicious lesion which scores ≥ 3 on either Likert or PI-RADS V.2.1. Four targeted cores will be taken per suspicious lesion, and these should be stored and labelled in separate containers to ensure cancer detection from separate suspicious areas is ascertained.

Systematic biopsy

Systematic biopsies should be performed after targeted biopsies, with six cores taken from the contralateral side of the MRI lesion, focused on sampling the peripheral zone of the prostate. If there are bilateral MRI lesions or midline lesions, then no systematic biopsies are necessary.

Table 2 Participant timeline in the trial: the timeline for men enrolled to the trial prior to undergoing MRI

	Contact with patient				
	Visit 0*	Visit 1	Visit 2	Visit 3	Visit 4
Screening	X	X			
PIS given	X	X			
Consent	X	X			
IIEF-5 and IPSS questionnaires	X	X			
mpMRI			X		
Radiologists report bpMRI (T2W and DWI only)			X		
Radiologists report mpMRI (T2W, DWI and DCE)			X		
MRI-targeted biopsy and systematic biopsy				X	
Test results given and treatment decision					X
Follow-up for further investigations from treatment decision					X
Serious adverse event	Complete as required at any time following registration				
Withdrawal form	Complete as required at any time following registration				

*Visit 0 is an optional teleconsult, depending on local practice. Note that, where applicable, more than one visit can take place on the same day, depending on local practice (eg, in centres where an MRI is performed on the same day as subsequent biopsies).
 bpMRI, biparametric MRI; DCE, dynamic contrast-enhanced sequence; DWI, diffusion-weighted sequence; IIEF-5, International Index of Erectile Function; IPSS, International Prostate Symptom Score; mpMRI, multiparametric MRI; PIS, patient information sheet; T2W, T2-weighted sequence.

Please see online supplemental appendix 2 for a detailed overview of how our biopsies will be conducted.

Prostate histopathology

Both the Gleason score and the Gleason grade group will be reported for the overall biopsy and for each individual target lesion.

Pre-trial assessments

For all patients, patient referral would follow clinical suspicion of PCa (eg, raised PSA or abnormal digital rectal examination). To confirm a patient's eligibility, screening will be undertaken. Patients can enter the trial either before or after they have had their mpMRI scan. If patients are recruited after an mpMRI scan has been carried out, this will only be permitted if the MRI has not been seen by any clinician.

Registration procedures

Following consent and confirmation of eligibility, trial processes can commence. The patient will be registered and assigned a trial ID using a central online database (Marvin by XClinical).

Intervention procedures

All patients will undergo a full mpMRI scan. This includes T2W, DWI and DCE sequences.

Follow-up for results

If bpMRI and mpMRI are non-suspicious and PSA density is <0.15 ng/mL/mL, the patient will be counselled for standard of care follow-up, typically consisting of PSA surveillance. If a decision for prostate biopsy or other

tests is made, these results will be recorded after which the participant completes the trial.

Multidisciplinary team (MDT) decision making for treatment eligibility

Treatment decisions will be per local standard of care, based on pathology results, and will be recorded. Subsequently, a virtual MDT meeting will be conducted and treatment eligibility decisions blinded to the DCE will be recorded. Once a decision has been recorded, the clinicians will be unblinded to the DCE sequence and the impact that this information makes on treatment eligibility will be evaluated.

MRI and pathology quality control

Quality control will be carried out at the end of the study by the PRIME chief radiologists reviewing the original MRIs, who will assess the MRI quality and re-report the MRI blinded to the study reports. Anonymised pathology slides from a proportion of patients may also be reviewed by central pathologists. Any slides assessed outside of the originating site will be returned to the original site after quality control. Quality control results will be reported but will not influence patient management or outcomes.

Cost-effectiveness

A within-trial incremental cost-effectiveness analysis will be conducted to calculate the difference in mean cost per diagnosis of clinically significant PCa if a strategy of bpMRI were adopted instead of the current mpMRI standard of care, over a time horizon of 30 days. The difference in cost of avoiding each additional case of clinically insignificant PCa diagnosed may also be calculated.

Table 3 Participant timeline in the trial: the timeline for men enrolled after undergoing mpMRI as part of routine care

	Contact with patient				
	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4
Screening		X			
PIS given		X			
Consent		X			
IIEF-5 and IPSS questionnaires	X				
mpMRI		X			
Radiologists report bpMRI (T2W and DWI only)		X			
Radiologists report mpMRI (T2W, DWI and DCE)		X			
MRI-targeted biopsy and systematic biopsy			X		
Test results given and treatment decision					X
Follow-up for further investigations from treatment decision					X
Serious adverse event	Complete as required at any time following registration				
Withdrawal form	Complete as required at any time following registration				

bpMRI, biparametric MRI; DCE, dynamic contrast-enhanced sequence; DWI, diffusion-weighted sequence; IIEF-5, International Index of Erectile Function; IPSS, International Prostate Symptom Score; mpMRI, multiparametric MRI; PIS, patient information sheet; T2W, T2-weighted sequence.

Costs of procedures will be estimated by applying standard unit costs to resource use data captured within the trial plus other procedures that would be offered to patients in either pathway. Estimates of the resources used (procedures, tests, radiotherapy, chemotherapy, other therapies, surveillance visits and other care events) on the two treatment pathways will be obtained for the theoretical bpMRI cohort using decisions made initially by the MDT with information from the bpMRI scan and any biopsies as a result of that scan, and estimates of the treatment pathway resources used in the theoretical mpMRI cohort will be made subsequently by the MDT on viewing additional information from the mpMRI scan and any further biopsies performed as a result of that scan. This thought experiment is required due to the ethical requirement to use all available information, that is, not just bpMRI and biopsies or just mpMRI and biopsies, when making the actual treatment decision with the patient.

The analysis perspective will be that of the NHS and personal social services. Standard unit costs (eg, NHS reference costs) will be supplemented by unit cost data from the participating trial sites. A microcosting study to provide this information will be undertaken in a small number of sites as part of the trial to investigate the resources employed to deliver bpMRI and mpMRI scans. This information will allow us to understand the MRI booking system, consumption of consumables and staff time as related to delivering bpMRI and mpMRI scans.

Depending on the within-trial cost-effectiveness findings, consideration will be given to extending this analysis using decision analytical modelling to estimate quality-adjusted life-years gained over a lifetime horizon. Quality of life information will be estimated from anonymised

patient-level data by the same group from an earlier study in this instance.

Outcomes

Primary outcome

The primary outcome will be the proportion of men with clinically significant PCa detected—any pattern 4 disease on any core (ie, Gleason score $\geq 3+4$ or Gleason grade group ≥ 2). The time frame for assessment will be when biopsy results are available, at an expected average of 30 days post biopsy.

Secondary outcomes

Table 1 lists our secondary outcomes.

Sample size

The margin of clinical unimportance to allow a conclusion of non-inferiority of bpMRI to mpMRI to be made was set at 5 percentage points; that is, if the lower bound of the 95% CIs for the difference in detection rates of bpMRI-targeted biopsy compared with mpMRI-targeted biopsy is above -5 percentage points, then bpMRI will be deemed as non-inferior.

Using simulation, we used an mpMRI underlying probability of detecting clinically significant cancer of 38%³ and the following two key probabilities to determine the sample size:

- ▶ The probability that a patient found to have no suspicious lesions on bpMRI or have no clinically significant PCa on bpMRI-targeted biopsy will have clinically significant PCa on mpMRI-targeted biopsy.
- ▶ The probability that a patient found to have no suspicious lesions on mpMRI or have no clinically

Table 4 WHO trial registration dataset

Data category	Information
Primary registry and trial identifying number	ClinicalTrials.gov: NCT04571840
Date of registration in the primary registry	1 October 2020
Sources of monetary or material support	<ul style="list-style-type: none"> ► Prostate Cancer UK. ► The John Black Charitable Foundation. ► European Association of Urology Research Foundation. ► The Dieckmann Foundation.
Primary sponsor	University College London
Secondary sponsor(s)	N/A
Contact for public queries	Mr Veeru Kasivisvanathan veeru.kasi@ucl.ac.uk Division of Surgery and Interventional Science, University College London, Third Floor, Charles Bell House, 43–45 Foley Street, London, W1W 7TS
Contact for scientific queries	Mr Veeru Kasivisvanathan veeru.kasi@ucl.ac.uk Division of Surgery and Interventional Science, University College London, Third Floor, Charles Bell House, 43–45 Foley Street, London, W1W 7TS
Public title/short title	Prostate Imaging Using MRI +/- Contrast Enhancement
Acronym	PRIME
Scientific title	A trial assessing whether bpMRI is non-inferior to multiparametric MRI in the diagnosis of clinically significant PCa
Countries of recruitment	Argentina Australia Belgium Brazil Canada Denmark France Finland Germany Italy The Netherlands Singapore Spain UK USA
Health condition or problem studied	Prostate neoplasm
Interventions	Device: MRI Diagnostic test: multiparametric MRI±prostate biopsy. Diagnostic test: bpMRI±prostate biopsy.
Intervention description	Active comparator: mpMRI.MRI with T2W, DWI and DCE followed by prostate biopsy if indicated on MRI and clinical findings. Diagnostic test: mpMRI±prostate biopsy.Experimental: bpMRI.MRI with T2W and DWI followed by prostate biopsy if indicated on MRI and clinical findings. Diagnostic test: bpMRI±prostate biopsy.
Key inclusion and exclusion criteria	<p>Inclusion criteria</p> <ul style="list-style-type: none"> ► Men at least 18 years of age referred with clinical suspicion of PCa. ► Serum PSA ≤20 ng/mL. ► Fit to undergo all procedures listed in the protocol. ► Able to provide written informed consent. <p>Exclusion criteria</p> <ul style="list-style-type: none"> ► Prior prostate biopsy. ► Prior treatment for PCa. ► Prior prostate MRI on a previous encounter. ► Contraindication to MRI. ► Contraindication to prostate biopsy. ► Unfit to undergo any procedures listed in the protocol.

Continued

Table 4 Continued

Data category	Information
Study type	Interventional Allocation: non-randomised Intervention model: single group assignment Intervention model description: within-person controlled, paired cohort, diagnostic evaluation study; participants undergo two index tests and a reference test Masking: single (care provider) Masking description: Radiologist assessing MRI for suspicion of PCa is blinded to the contrast sequence when reporting the bpMRI. After this report, they are unblinded to the contrast sequence and report the multiparametric MRI. All biopsies conducted as a result of MRI findings will be labelled as bpMRI and mpMRI, and diagnostic accuracy will be assessed against histological findings.
Date of first enrolment	5 April 2022
Target sample size	500
Recruitment status	Recruiting
Primary outcome(s)	Proportion of men with clinically significant cancer
Key secondary outcomes	<ul style="list-style-type: none"> ▶ Proportion of men with clinically insignificant cancer (Gleason score 3+3/Gleason grade group 1). ▶ Agreement between bpMRI and mpMRI for score of suspicion. ▶ Proportion of bpMRI scans and mpMRI whose quality was deemed adequate for reporting. ▶ Agreement between bpMRI and mpMRI for radiological staging decision. ▶ Agreement between bpMRI and mpMRI for treatment eligibility. ▶ Test performance characteristics for bpMRI and mpMRI when using the Likert scoring system in comparison to the PI-RADS scoring system. ▶ Proportion of men with clinically significant cancer missed by bpMRI and mpMRI-targeted biopsies and detected by systematic biopsy. ▶ Cost-effectiveness of bpMRI compared with mpMRI (cost per diagnosis of PCa).

bpMRI, biparametric MRI; DCE, dynamic contrast-enhance sequence; DWI, diffusion-weighted sequence; mpMRI, multiparametric MRI; PCa, prostate cancer; PRIME, Prostate Imaging Using MRI±Contrast Enhancement; T2W, T2-weighted sequence.

significant PCa on mpMRI-targeted biopsy will have clinically significant PCa on bpMRI-targeted biopsy.

Assuming the probability of A is greater than the probability of B, and applying McNemar's test in each of 1000 simulation runs for each combination of probabilities A and B ranging from 0 to 0.05, a sample size of 400 patients gives more than 90% power across these probabilities of A and B. Accounting for 20% dropout or exclusion after enrolment, the study will require at least 500 patients.

Recruitment

At each participating site, enrolment will occur at outpatient clinics. With at least 25 sites, it is estimated that the trial will complete within 24 months of commencement. The trial opened for recruitment in April 2022 and the estimated completion date is April 2024.

Data collection methods

The electronic case report form (eCRF) system Marvin by XClinical will be used to collect data.

Patient-reported outcome measures

The International Index of Erectile Function and the International Prostate Symptom Score will be used to assess baseline erectile function and lower urinary tract symptoms, respectively. These questionnaires will aid the MDT decision making for treatment eligibility.

Patient retention

It is estimated that loss to follow-up will be no more than 20% due to the expected short time interval between enrolment and end of study. It is expected that the majority of patients will complete the trial within 4–6 weeks (tables 2 and 3).

Table 5 Revision chronology for amendments to protocol

Protocol version to date	Reasons for amendments
V.1.0, issued 24 August 2020	Original protocol
V.2.0, issued 27 April 2021	<p>Main reasons for amendment: minor changes to make existing trial documents clearer. Main changes:</p> <ul style="list-style-type: none"> ▶ Updated Section 18 Record Keeping and Archiving. Added the sentence, 'Identifiable data will be kept by the site for 10 years, and non-identifiable data will be kept for a minimum of 20 years'. ▶ Version number and date added to all pages.

Table 6 Roles and responsibilities in the prime trial

Role	Details and responsibilities
Trial sponsor	<p>University College London (UCL) Sponsor's Edge reference: 135819 Email: Rand.D@uclh.nhs.uk</p> <p>The trial sponsor did not provide any funding for the study. UCL has the role of research governance sponsor of PRIME. UCL adopted the study as sponsor after the UCL CCTU carried out a trial adoption process which involved the UCL CCTU reviewing the protocol to ensure it conformed to high standards of trial conduct and met the governance requirements of UCL. The UCL CCTU is responsible for oversight of the trial. The sponsor plays no role in data collection, management, analysis and interpretation of data, writing of the report or the decision to submit the report for publication.</p>
PRIME operations group	<p>The PRIME operations group consists of the CI, the Clinical Operations Group, National Cancer Imaging Translational Accelerator, the UCL Surgical and Interventional Trials Unit and the electronic case report form database managers. This group is responsible for</p> <ul style="list-style-type: none"> ► Study planning. ► Preparation of protocol and revisions. ► Assistance with international review board/independent ethics committee applications. ► Preparation of investigators brochure and CRFs. ► Organisation of steering committee meetings. ► Provide annual progress reports to the ethics committee. ► Reporting serious adverse events to the sponsor and ethics committee when necessary. ► Responsible for trial master file. ► Budget administration and contractual issues with individual centres. ► Advice for PIs. ► Site initiation visits. ► Data verification and management. ► Central monitoring and resolving data queries with clinicians and nurses at the trial sites. ► Maintenance of the trial information technology system. ► Publication of study reports.
PI	<p>At each participating site, the PI is responsible for the conduct of the clinical trial to ensure the safety of participants and the reliability and robustness of the data generated. They will be responsible for identification, recruitment, data collection and completion of CRFs, along with follow-up of trial patients and adherence to trial protocol. The PIs as leader of the research team may delegate their duties to members of their team.</p>
Global TSC	<p>The NCITA global prostate TSC is responsible for the governance of the PRIME study, and they have delegated safety to a DMSC.</p> <p>Roles and responsibilities</p> <p>To act as the oversight body for up to five prostate cancer studies on behalf of the sponsor and funders. In addition, the independent members will form a subcommittee to review safety. The role of the TSC is to provide oversight for the studies and provide advice through its chair to the CIs, work in tandem with the DMSC, sponsor, funders and host institution on all aspects of the studies. The rights, safety and well-being of the study participants are the most important consideration and should prevail over the interests of science and society.</p>

CCTU, Comprehensive Clinical Trials Unit; CI, chief investigator; DMSC, data monitoring subcommittee; PI, principal investigator; TSC, trial steering committee; UCL, University College London.

Statistical methods

A statistical analysis plan will be finalised before our database lock and before any statistical analysis occurs. A consort diagram will be presented. All continuous variables will be described using the mean and SD, or median and IQR, as appropriate. Categorical variables will be described using frequencies and percentages. Baseline characteristics will be examined and presented for those with and those without clinically significant PCa. The assumptions underpinning the statistical methods used will be assessed. The use of transformations will be considered to satisfy statistical assumptions.

Primary outcome analysis

The primary outcome is the difference in the proportion of men with clinically significant PCa, as detected by bpMRI-targeted biopsy compared with mpMRI-targeted biopsy. The proportion of men with clinically significant PCa, Gleason score of $\geq 3+4$ or Gleason grade group of ≥ 2 , detected by bpMRI-targeted biopsy, is defined as the number of men with clinically significant PCa identified on bpMRI-targeted biopsy divided by the number of men undergoing bpMRI. Similarly, the proportion of men with clinically significant PCa detected by mpMRI-targeted biopsy is defined as the number of men with clinically

significant PCa identified on mpMRI-targeted biopsy divided by the number of men undergoing mpMRI. Methods that account for the paired nature of the data such as McNemar's test will be used to compare bpMRI and mpMRI.

Secondary outcome analysis

The proportion of men with clinically insignificant cancer (any cancer core with Gleason score 3+3 or Gleason grade group 1) detected by bpMRI-targeted biopsy will be compared with that of mpMRI-targeted biopsy. The proportion of men with clinically insignificant cancer detected by bpMRI-targeted biopsy is defined as the number of men with clinically insignificant PCa identified on bpMRI-targeted biopsy divided by the number of men undergoing bpMRI. Similarly, the proportion of men with clinically insignificant cancer detected by mpMRI-targeted biopsy is defined as the number of men with clinically insignificant PCa identified on mpMRI-targeted biopsy divided by the number of men undergoing mpMRI. The same analytical approach described for clinically significant PCa will be applied.

The number and proportion of men scoring 1 or 2 (non-suspicious) or 3 (indeterminate) on bpMRI and mpMRI will be reported. A two-way table will be produced to show the agreement between the two MRI results using the Likert scoring system on a scale of 1–5.

The number and proportion of men with adequate standard of reporting on bpMRI and mpMRI will be reported.

A two-way table will be produced to show the number and proportion of patients with each radiological stage of bpMRI and mpMRI. Similarly, we will report the number and proportion of patients eligible for different treatment options following discussion of the bpMRI and mpMRI results in the MDT meeting.

Using histopathology as the reference standard, sensitivity, specificity, positive predictive value and negative predictive value with 95% CI of bpMRI and mpMRI will be reported. The following assumptions will be made, where non-suspicious MRI refers to a score of 1 or 2; suspicious MRI refers to a score of 3, 4 or 5 on the Likert and PI-RADS V.2.1 scoring systems; and absence of clinically significant cancer refers to a combination of clinical insignificant and no cancer.

The number and proportion of men with clinically significant cancer detected by systematic biopsy and not detected by bpMRI and mpMRI with targeted biopsy will be reported. A two-way table will be produced to show a comparison between systematic biopsy (no biopsy, clinically significant cancer, clinically insignificant cancer and no cancer) and the two MRI results with targeted biopsy (no biopsy, clinically significant cancer, clinically insignificant cancer and no cancer).

Sensitivity and other planned analyses

The primary outcome analysis will be repeated with a definition of clinically significant PCa being any primary

pattern 4 disease with a Gleason score of 4+3 or a Gleason grade group of 3.

Monitoring

The National Cancer Imaging Translational Accelerator (NCITA) Global Prostate Trial Steering Committee (TSC) is responsible for the governance of the PRIME Study. A subgroup of independent TSC members form the data monitoring subcommittee (DMSC).

Roles and responsibilities of the TSC

The TSC's role is to act as the oversight body for up to five PCa studies on behalf of the sponsor and funders. In addition, the independent members will form a DMSC to review safety. The role of the TSC is to provide oversight for the studies and advice through its chair to the chief investigators while working in tandem with the DMSC, sponsor, funders and host institution on all aspects of the studies. The rights, safety and well-being of the study participants are the most important consideration and should prevail over the interests of science and society.

Harms

Adverse events (AEs) will be defined as 'any untoward medical occurrence in a clinical trial subject undergoing any intervention in the trial, which does not necessarily have a causal relationship with this treatment'.

Serious adverse events (SAEs) will be defined as 'any untoward medical occurrence as a result of any intervention in the trial that:

- ▶ Results in death,
- ▶ Is life-threatening
- ▶ Requires hospitalisation or prolongation of existing inpatients' hospitalisation, results in persistent or significant disability or incapacity'.

AEs and SAEs will be recorded until 30 days post biopsy. In the event that the patient does not undergo biopsy, AEs and SAEs should be recorded until 30 days post MRI.

Unexpected AEs will be recorded by a member of the research team or clinical team on an AE report form or eCRF. All SAEs must be recorded on an SAE report form or eCRF, which must be sent to the coordinating trial unit within 24 hours of knowledge of the SAE. Both AEs and SAEs should be recorded in the medical notes.

Ethics and approval

The UK National REC (West Midlands Black Country Research Ethics Committee, Nottingham) gave favourable approval for PRIME protocol V.2.0 on 28 June 2021 (ref: 21/WM/0091). All participating centres have gained local and ethical approvals prior to receiving a site initiation visit and approval by the sponsor to open for recruitment.

Patient and public involvement

Patients and public members were involved in defining the research question, evaluation of the research proposal, suggesting modifications to the trial, reviewing the patient information sheet, consent form and general

practitioner letter. Patient groups and charities will also be involved in the dissemination of results.

Consent

The clinical teams managing patients with suspected PCa who are referred to their centre will identify potential trial participants. Patient information sheets will be provided to patients. Members of staff who are trained to obtain informed consent, as indicated by the principal investigator (PI) on the delegation log for that site, will obtain the informed consent. A model patient information sheet is shown in online supplemental appendix 3.

Confidentiality

The data of the participants will be recorded into the eCRF system and analysed without any personal identifiers by pseudoanonymised coded information. A site's source documents and identification lists will be archived in a secured facility at that centre.

Dissemination

Results of this trial will be disseminated through national and international conferences and papers. Authorship criteria will be based on recommendations of the International Committee of Medical Journal Editors. The participants and relevant patient support groups will be informed about the results of the trial.

Access to data

Only authorised individuals within the PRIME Clinical Operations Group have access to the final data set. Individual PIs have access to their own data but not that of other sites.

WHO Trial Registration Dataset

Please see [table 4](#) for the WHO trial registration dataset.

Current Protocol Version

The current protocol is V.2.0, issued 27 April 2021. The current protocol amendment number is 01. For full amendment history, please see [table 5](#).

Roles and Responsibilities

Please see [table 6](#) for roles and responsibilities of the trial sponsor and involved committees.

Author affiliations

¹Division of Surgery and Interventional Science, University College London, London, UK

²Clinical Effectiveness Unit, Royal College of Surgeons of England, London, UK

³Department of Urology, Whipps Cross University Hospital, London, UK

⁴Department of Radiology, University College London Hospitals NHS Foundation Trust, London, UK

⁵Department of Histopathology, University College London Hospitals NHS Foundation Trust, London, UK

⁶Centre for Medical Imaging, University College London, London, UK

⁷Institute of Epidemiology and Health Care, University College London, London, UK

⁸School of Population Health, The University of Auckland, Auckland, New Zealand

⁹Research Department of Primary Care and Population Health, University College London, London, UK

¹⁰National Cancer Imaging Translational Accelerator, University College London, London, UK

¹¹Department of Urology, University College London Hospitals NHS Foundation Trust, London, UK

¹²Test Evaluation Research Group, Institute of Applied Health Research, University of Birmingham, Birmingham, UK

¹³NIHR Birmingham Biomedical Research Centre, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

Twitter Aqua Asif @AquaAsif, Arjun Nathan @ArjunSNathan, Alexander Ng @AlexBCDNg, Pramit Khatri @p_khatri, Vinson Wai-Shun Chan @VinsonChan, Francesco Giganti @giga_fra, Shonit Punwani @ShonitP, Mark Emberton @EmbertonMark, Jonathan J Deeks @deeksj, Caroline M Moore @mrsprostata, Veeru Kasivisvanathan @veerukasi and PRIME Trial Group @PrimeMRI

Acknowledgements We would like to thank our patients and funders, without whom we wouldn't be able to carry out this important study: Prostate Cancer UK, The John Black Charitable Trust, European Association of Urology Research Foundation and the Dieckmann Foundation. We thank all the international centres taking part in PRIME. We are grateful to EAU Research Foundation and the XClinical team for their support with the MARVIN database; and Sydney Lindner, Steven Lelie, Jessica Sternisa, Tyler Edwards, Adam Kulp, Jon Piper from the MIM Software Inc team. We are thankful for the trial oversight provided by our sponsor, University College London and the National Cancer Imaging Translational Accelerator trials unit.

Collaborators PRIME Trial Group: John Wilkinson, Marimo Rossiter, Réka Novotná, Philip Ryan, Alex Kirkham, Louise Dickinson, Tushar Narain, Hazel McBain, Antonette Andrews, Daniel Margolis, Valeria Panebianco, Antti Rannikko, Peter Albertsen, Lance Mynderse, Adam Froemming, Naoki Takahashi, Tristan Barrett, Raphaële Renard-Penna, Vibeke Løgager, Lars Boesen, Sangeet Ghai, Lars Budäus, Enrique Gómez Gómez, Jeremy Grummet, Tho Pham, Aiman Haider, Jing Yi Jessica Weng, Anders Bjartell, Wim Witjes, Christien Caris, Joke Van Egmond.

Contributors Study concept and design: ANg, AA, AN, VC, PK, FG, CA, AF, SP, PL, CSC, CBG, NM, ME, RA, YT, JD, CMM, VK. Drafting of manuscript: AA, AN, CSC, CBG, RA, YT, VK. Critical revision of the manuscript for important intellectual content: all authors. Supervision: CA, VK. All authors read and approved the final manuscript.

Funding The PRIME trial is primarily funded by Prostate Cancer UK (grant number: TLD-PF19-004) and The John Black Charitable Trust Travelling Prize Grant (grant number: TLD-PF19-004). The EAU Research Foundation (EAU RF) and The Dieckmann Foundation also supported costs for international sites.

Competing interests AN is an academic clinical fellow funded by the National Institute for Health and Care Research. PK is an academic clinical fellow funded by the National Institute for Health and Care Research and The Urology Foundation. FG is a recipient of the 2020 Young Investigator Award (20YOUN15) funded by the Prostate Cancer Foundation / CRIS Cancer Foundation. SP is supported by the National Institute of Health and Care Research (NIHR), UCLH and UCL Biomedical Research Centre. ME receives research support from the National Institute of Health and Care Research (NIHR), UCLH and UCL Biomedical Research Centre. YT is funded by a UK NIHR Postdoctoral Fellowship and supported by the NIHR Birmingham Biomedical Research Centre. CMM is an NIHR Research Professor, and receives grants from MRC, CRUK, Movember, and Prostate Cancer UK. VK is funded by Prostate Cancer UK and The John Black Charitable Foundation. He receives speaker fees from the European Association of Urology, Singapore Urology Association, The Clinical Comms Group and Got IT consulting SL. All authors declare that there are no conflicts of interest. The views expressed in this publication are those of the authors and not necessarily those of the National Health Service, NIHR, or the Department of Health and Social Care.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Ethical approval was obtained from the National Research Ethics Committee West Midlands, Nottingham 21/WM/0091 on 28th June 2021. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; peer reviewed for ethical and funding approval prior to submission.

Data availability statement Data sharing not applicable as no datasets generated and/or analysed for this Protocol.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution 4.0 Unported (CC BY 4.0) license, which permits others to copy, redistribute, remix, transform and build upon this work for any purpose, provided the original work is properly cited, a link to the licence is given, and indication of whether changes were made. See: <https://creativecommons.org/licenses/by/4.0/>.

ORCID iDs

Aqua Asif <http://orcid.org/0000-0003-3233-7428>

Arjun Nathan <http://orcid.org/0000-0002-8572-2832>

Caroline S Clarke <http://orcid.org/0000-0002-4676-1257>

Mark Emberton <http://orcid.org/0000-0003-4230-0338>

Ridhi Agarwal <http://orcid.org/0000-0002-6930-5617>

Caroline M Moore <http://orcid.org/0000-0003-0202-7912>

Veeru Kasivisvanathan <http://orcid.org/0000-0002-0832-382X>

REFERENCES

- Chan A-W, Tetzlaff JM, Gøtzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586.
- Mottet N, Cornford P, Van Den Bergh R, et al. EAU guidelines: prostate cancer. European Association of Urology, Arnhem, The Netherlands; 2021. Available: <https://uroweb.org/guideline/prostate-cancer/>
- 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.
- National prostate cancer audit. Annual Report 2019; Available: <https://www.npca.org.uk/reports/npca-annual-report-2019/>
- Verma S, Turkbey B, Muradyan N, et al. Overview of dynamic contrast-enhanced MRI in prostate cancer diagnosis and management. *AJR Am J Roentgenol* 2012;198:1277–88.
- Berman RM, Brown AM, Chang SD, et al. DCE MRI of prostate cancer. *Abdom Radiol (NY)* 2016;41:844–53.
- Engelbrecht MR, Huisman HJ, Laheij RJF, et al. Discrimination of prostate cancer from normal peripheral zone and central gland tissue by using dynamic contrast-enhanced MR imaging. *Radiology* 2003;229:248–54.
- van der Leest M, Cornel E, Israël B, et al. Head-to-head comparison of transrectal ultrasound-guided prostate biopsy versus multiparametric prostate resonance imaging with subsequent magnetic resonance-guided biopsy in biopsy-naïve men with elevated prostate-specific antigen: a large prospective multicenter clinical study. *Eur Urol* 2019;75:570–8.
- Fraum TJ, Ludwig DR, Bashir MR, et al. Gadolinium-Based contrast agents: a comprehensive risk assessment. *J Magn Reson Imaging* 2017;46:338–53.
- Ramalho M, Ramalho J, Burke LM, et al. Gadolinium retention and toxicity—an update. *Adv Chronic Kidney Dis* 2017;24:138–46.
- Boesen L, Nørgaard N, Løgager V, et al. Assessment of the diagnostic accuracy of biparametric magnetic resonance imaging for prostate cancer in biopsy-naïve men: the biparametric MRI for detection of prostate cancer (BIDOC) study. *JAMA Netw Open* 2018;1:e180219.
- Kang Z, Min X, Weinreb J, et al. Abbreviated biparametric versus standard multiparametric MRI for diagnosis of prostate cancer: a systematic review and meta-analysis. *American Journal of Roentgenology* 2019;212:357–65.
- Alabousi M, Salameh J-P, Gusenbauer K, et al. Biparametric vs multiparametric prostate magnetic resonance imaging for the detection of prostate cancer in treatment-naïve patients: a diagnostic test accuracy systematic review and meta-analysis. *BJU Int* 2019;124:209–20.
- Ng A, Khetrapal P, Kasivisvanathan V. Is it prime time for biparametric magnetic resonance imaging in prostate cancer diagnosis? *Eur Urol* 2022;82:1–2.
- Giganti F, Allen C, Emberton M, et al. Prostate imaging quality (PI-QUAL): a new quality control scoring system for multiparametric magnetic resonance imaging of the prostate from the precision trial. *Eur Urol Oncol* 2020;3:615–9.
- Weinreb JC, Barentsz JO, Choyke PL, et al. PI-RADS prostate imaging - reporting and data system: 2015, version 2. *Eur Urol* 2016;69:16–40.

TRIAL IDENTIFIER:

PARTICIPANT INITIALS:

Reporting Proforma (bpMRI):

Report 1 – Biparametric MRI (bpMRI) Report

This report should be completed **without looking at the contrast sequence.**

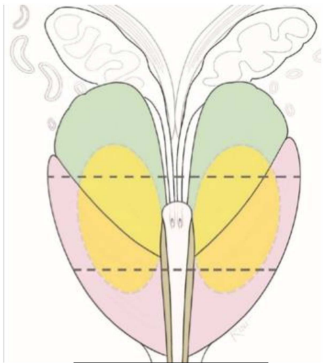
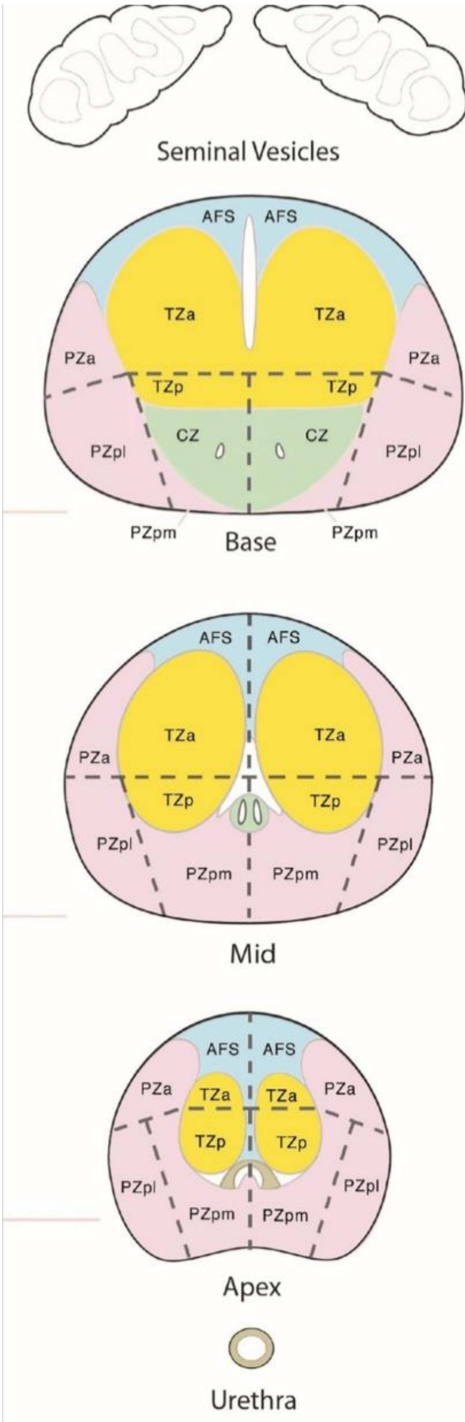
If applicable, complete the Target boxes & link these to your drawings of the Targets (e.g. with lines / colours)

Target 1	Likert:
	PIRADS:

Target 2	Likert:
	PIRADS:

Target 3	Likert:
	PIRADS:

Target 4	Likert:
	PIRADS:



Coronal plane

Reminder of Likert Score: Likelihood of target containing significant cancer:

- 1 = Highly unlikely
- 2 = Unlikely
- 3 = Equivocal
- 4 = Likely
- 5 = Highly Likely

In the case of diffuse changes on **both sides** of the prostate scoring ≥ 3 (Likert), the diffuse changes on each side of the prostate can be arbitrarily treated as **separate targets**. "Diffuse change" is defined as an intermediate or low T2 signal that occupies the majority of at least one side of the peripheral zone, without a defined border



TRIAL IDENTIFIER:

PARTICIPANT INITIALS:

1. Radiologists should **first** annotate, draw and label the diagram on the first page with **up to 3** suspicious areas scoring ≥ 3 on the Likert scale (L) of suspicion (1–5). Clinical information is permitted to be used to influence the score.
2. Radiologists should then score suspicious areas **strictly** using the PI-RADS v2.1 (P) criteria, **without** allowing clinical information to influence the score.
3. If an additional area of suspicion is identified when scoring with PI-RADS v2.1 that was **not** present on Likert, please draw on this 4th suspicious area.

A maximum of **4 targets** can be drawn on this report.

1. Every lesion **must have both** a Likert and PI-RADS v2.1 score marked on.
2. Mark the **most suspicious** area, "Target 1".
 - a. Mark the **next most suspicious area**, "Target 2".
 - b. Mark the **subsequent most suspicious area**, "Target 3" and so on.
3. **On the diagram above, every** lesion drawn must have the following marked and labelled:
 - a. Target number
 - b. Likert score
 - c. PI-RADS v2.1 score
4. Please then insert these into **Table 1** and fill out the rest of the proforma.

e.g. Target 1. Likert 3. PI-RADS 1.

MRI Scanner and Clinical Information

Patient age (years):		PSA (ng/ml):		Which MRI scanner was used? 1. <input type="checkbox"/> SCANNER ONE 2. <input type="checkbox"/> SCANNER TWO 3. <input type="checkbox"/> SCANNER THREE
MRI volume of prostate (ml):		PSA Density (ng/ml/ml):		
Field Strength of Magnet	<input type="checkbox"/> 1.5T <input type="checkbox"/> 3T			

Confirmation of blinding

Confirmation by another individual / system that the radiologist is blinded to DCE images (mandatory)	<input type="checkbox"/> Yes <input type="checkbox"/> No
---	--

TRIAL IDENTIFIER:

PARTICIPANT INITIALS:

Table 1. Please only enter Targets below if the Likert or PI-RADS v2.1 score is ≥ 3 .

TARGET SPECIFIC INFORMATION	TARGET 1	TARGET 2	TARGET 3	TARGET 4
Location of suspicious area(s) (select one option):	<input type="checkbox"/> Right <input type="checkbox"/> Left <input type="checkbox"/> Bilateral	<input type="checkbox"/> Right <input type="checkbox"/> Left <input type="checkbox"/> Bilateral	<input type="checkbox"/> Right <input type="checkbox"/> Left <input type="checkbox"/> Bilateral	<input type="checkbox"/> Right <input type="checkbox"/> Left <input type="checkbox"/> Bilateral
Location in prostate according to PI-RADS v2.1 41-sector diagram (select the one main location which contains the target):	<input type="checkbox"/> Base <input type="checkbox"/> Mid <input type="checkbox"/> Apex <input type="checkbox"/> Seminal Vesicle	<input type="checkbox"/> Base <input type="checkbox"/> Mid <input type="checkbox"/> Apex <input type="checkbox"/> Seminal Vesicle	<input type="checkbox"/> Base <input type="checkbox"/> Mid <input type="checkbox"/> Apex <input type="checkbox"/> Seminal Vesicle	<input type="checkbox"/> Base <input type="checkbox"/> Mid <input type="checkbox"/> Apex <input type="checkbox"/> Seminal Vesicle
Main sector which contains the lesion according to PI-RADS v2.1 41-sector diagram (write one , e.g. "PZpl"):				
Likert score of suspicion (1–5):				
PI-RADS v2.1 score of suspicion (1–5):				
Target appearance (select one): The default is focal, unless there is diffuse change in the peripheral zone	<input type="checkbox"/> Focal <input type="checkbox"/> Diffuse	<input type="checkbox"/> Focal <input type="checkbox"/> Diffuse	<input type="checkbox"/> Focal <input type="checkbox"/> Diffuse	<input type="checkbox"/> Focal <input type="checkbox"/> Diffuse
Biaxial diameter on sequence where it was largest, in axial plane (mm x mm):				
Sequence used to measure biaxial diameter (select one):	<input type="checkbox"/> T2 <input type="checkbox"/> High b <input type="checkbox"/> ADC	<input type="checkbox"/> T2 <input type="checkbox"/> High b <input type="checkbox"/> ADC	<input type="checkbox"/> T2 <input type="checkbox"/> High b <input type="checkbox"/> ADC	<input type="checkbox"/> T2 <input type="checkbox"/> High b <input type="checkbox"/> ADC

Please complete the **overall scores** regardless of whether there are any Targets identified above:

Overall patient Likert score Enter the highest Likert score		Overall patient PIRADS v2.1 score Enter the highest PI-RADS v2.1 score	
---	--	--	--

If there are no Targets scoring ≥ 3 on either scoring system, then the overall Likert and PI-RADS v2.1 score will be 1 or 2.

TRIAL IDENTIFIER:

PARTICIPANT INITIALS:

Table 2. Staging information. Complete **only** if a Target has been identified above:

Radiological stage:	<input type="checkbox"/> T2a <input type="checkbox"/> T2b <input type="checkbox"/> T2c <input type="checkbox"/> T3a <input type="checkbox"/> T3b <input type="checkbox"/> T4 Radiological T3a = unequivocal extracapsular disease				
Likelihood of right -sided extracapsular spread *: 1 = highly unlikely , 3 = equivocal, 5 = highly likely	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
Likelihood of left -sided extracapsular spread *:	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
Likelihood of right seminal vesicle involvement:	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
Likelihood of left seminal vesicle involvement:	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
Likelihood of urethral sphincter involvement:	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
Likelihood of bladder neck involvement:	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
Likelihood of rectal involvement:	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

* See PI-RADS v2.1 guidelines for examples of features suggestive of extracapsular spread.

MRI Quality: Please **complete** this for **all** MRIs regardless of whether a Target was identified:

Was there a problem with the quality of the T2W sequence?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Was there a problem with the quality of the DWI sequence?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
If there were problems, please describe these (tick all that apply): For T2W: For DWI:	<input type="checkbox"/> Rectal air <input type="checkbox"/> Movement artefact <input type="checkbox"/> Prosthesis <input type="checkbox"/> Other <input type="checkbox"/> Rectal air <input type="checkbox"/> Movement artefact <input type="checkbox"/> Prosthesis <input type="checkbox"/> Other	
If other, please describe:		
Was the quality of the scan sufficient for you to make a diagnostic assessment?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Hypothetically, if this patient only had this biparametric MRI scan:		
• Would you typically have recommended a repeat bpMRI ?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
• Would you typically have recommended a contrast sequence to be done?	<input type="checkbox"/> Yes	<input type="checkbox"/> No

Radiologist (Forename, Surname):	Date of MRI:	
	Date of Report:	

TRIAL IDENTIFIER:

PARTICIPANT INITIALS:

Reporting Proforma (mpMRI):

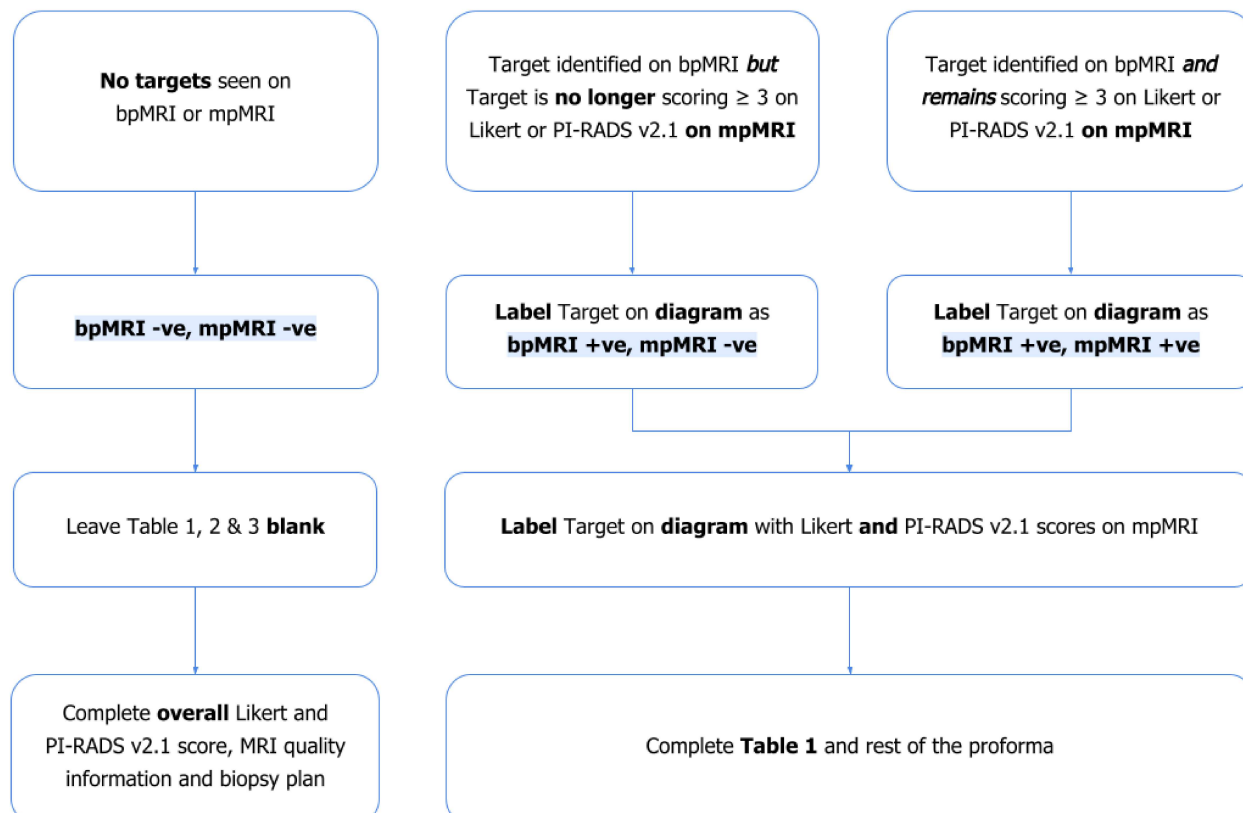
Report 2 – Multiparametric MRI (mpMRI) Report

The same radiologist should annotate the diagrams below after they are **unblinded** to the **DCE sequence**. This report will be used by the biopsy operator to perform **targeted biopsy**.

A total of **maximum 8 suspicious areas scoring ≥ 3 on either Likert or PI-RADS v2.1** can be annotated in this report.

PART ONE: TARGETS SEEN ON BPMRI

- First, copy any targets drawn on **Report 1** (bpMRI) onto this report (**Report 2 – mpMRI**).
 - Draw them on the diagram.
 - Specify their biparametric MRI status (bpMRI +ve or bpMRI -ve) when you label each lesion.
 - Add the information about each target to **Table 1** as indicated.
- Upon viewing the **DCE findings**, for each of these lesions, please specify their multi-parametric MRI status (mpMRI +ve or mpMRI -ve) on the diagram then specify **updated** Likert (L) and PI-RADS v2.1 (P) scores on mpMRI.

Flow diagram: how to complete this proforma for lesions identified on bpMRI (Report 1)

TRIAL IDENTIFIER:

PARTICIPANT INITIALS:

Please draw any Targets on this diagram
and label them according to the flow diagram on Page 1

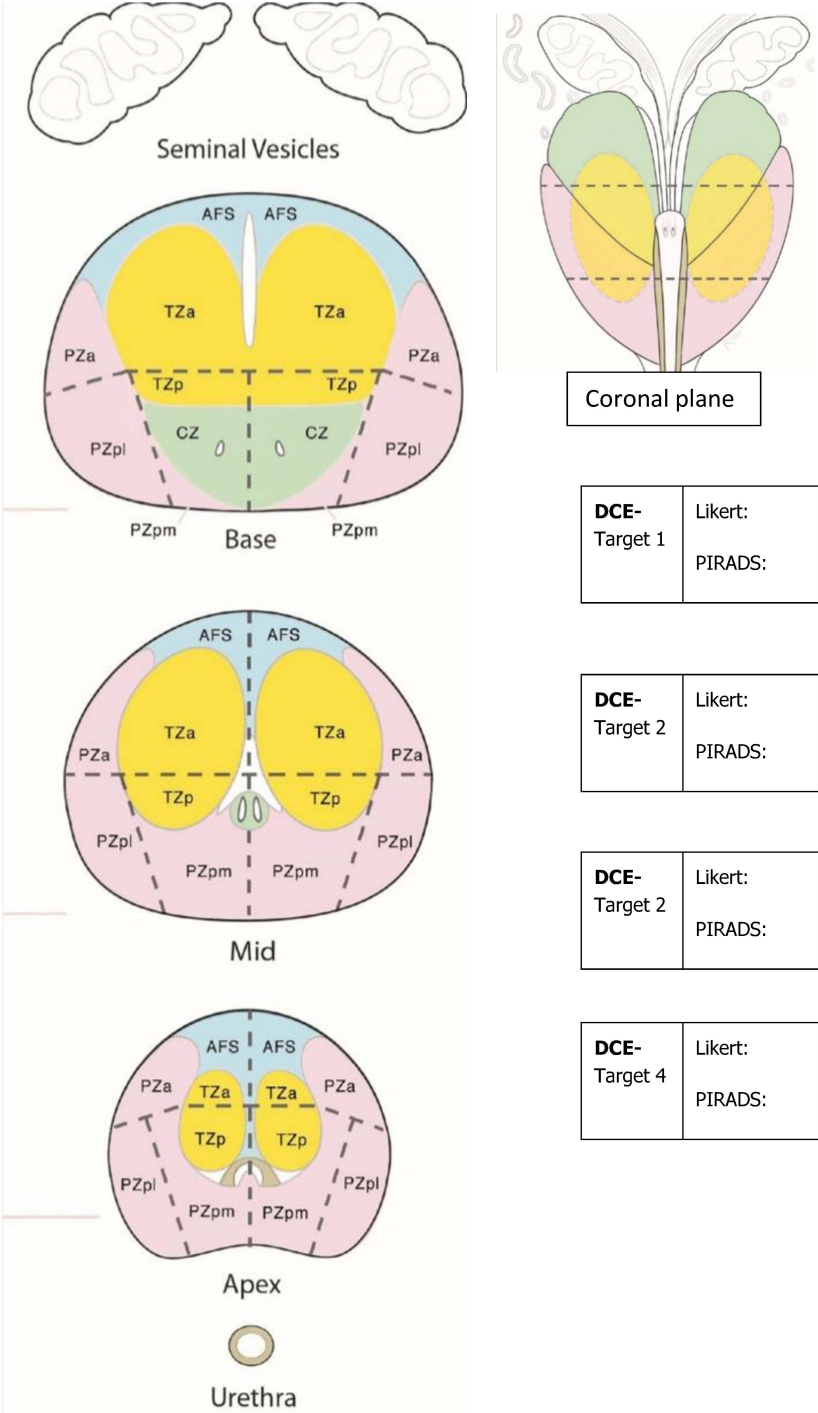
If applicable, complete the
Target boxes & link these to
your drawings of the Targets
(e.g. with lines / colours)

Target 1	bpMRI	mpMRI
	Likert:	Likert:
	PIRADS:	PIRADS:

Target 2	bpMRI	mpMRI
	Likert:	Likert:
	PIRADS:	PIRADS:

Target 3	bpMRI	mpMRI
	Likert:	Likert:
	PIRADS:	PIRADS:

Target 4	bpMRI	mpMRI
	Likert:	Likert:
	PIRADS:	PIRADS:



Coronal plane

DCE- Target 1	Likert:
	PIRADS:

DCE- Target 2	Likert:
	PIRADS:

DCE- Target 2	Likert:
	PIRADS:

DCE- Target 4	Likert:
	PIRADS:

In the case of diffuse changes on **both sides** of the prostate scoring ≥ 3 (Likert), the diffuse changes on each side of the prostate can be arbitrarily treated as **separate Targets**. "Diffuse change" is defined as an intermediate or low T2 signal that occupies the majority of at least one side of the peripheral zone, without a defined border.



TRIAL IDENTIFIER:

PARTICIPANT INITIALS:

MRI Scanner and Clinical Information. Complete for all patients:

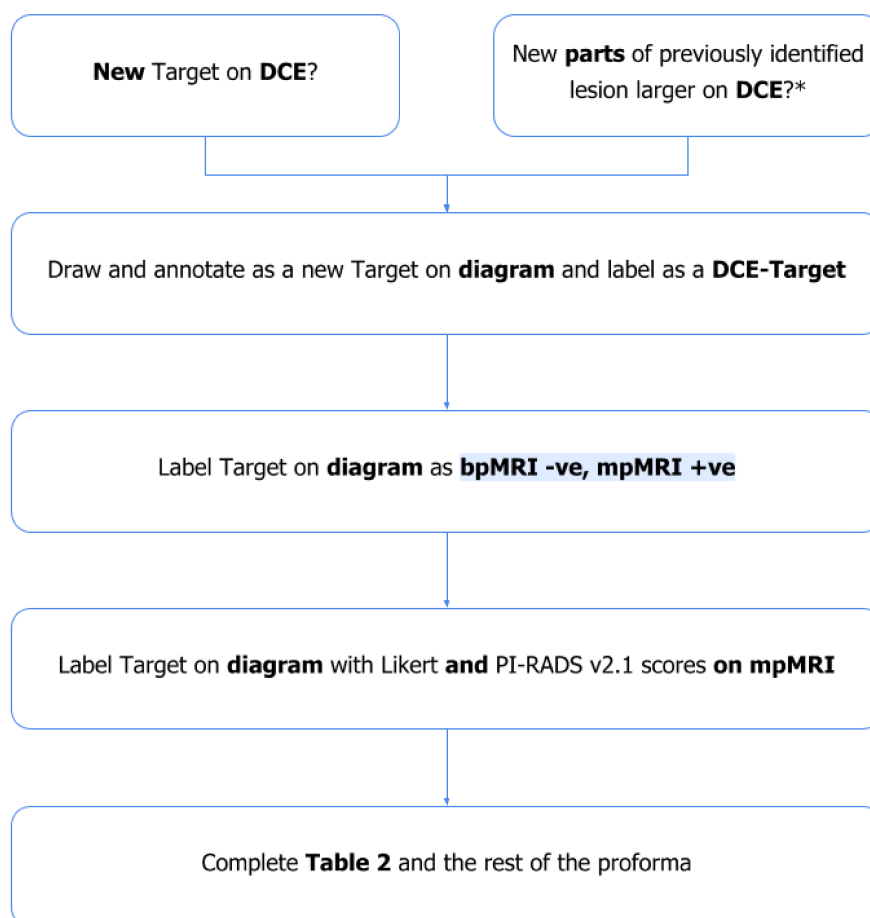
Patient age (years)		PSA (ng/ml):		
MRI volume of prostate (ml):		PSA Density (ng/ml/ml):		

Table 1. Information from Targets **originally** identified on the **biparametric MRI** (if applicable):

TARGET SPECIFIC INFORMATION	TARGET 1	TARGET 2	TARGET 3	TARGET 4
COPY FROM REPORT 1 (BPMRI):				
Location of suspicious area(s) (select one option):	<input type="checkbox"/> Right <input type="checkbox"/> Left <input type="checkbox"/> Bilateral	<input type="checkbox"/> Right <input type="checkbox"/> Left <input type="checkbox"/> Bilateral	<input type="checkbox"/> Right <input type="checkbox"/> Left <input type="checkbox"/> Bilateral	<input type="checkbox"/> Right <input type="checkbox"/> Left <input type="checkbox"/> Bilateral
Location in prostate according to PI-RADS v2.1 41-sector diagram (select the one main location which contains the target):	<input type="checkbox"/> Base <input type="checkbox"/> Mid <input type="checkbox"/> Apex <input type="checkbox"/> Seminal Vesicle	<input type="checkbox"/> Base <input type="checkbox"/> Mid <input type="checkbox"/> Apex <input type="checkbox"/> Seminal Vesicle	<input type="checkbox"/> Base <input type="checkbox"/> Mid <input type="checkbox"/> Apex <input type="checkbox"/> Seminal Vesicle	<input type="checkbox"/> Base <input type="checkbox"/> Mid <input type="checkbox"/> Apex <input type="checkbox"/> Seminal Vesicle
Main sector which contains the lesion according to PI-RADS v2.1 41-sector diagram (write one sector, <i>e.g.</i> "PZpl"):				
Biparametric MRI Likert score (1–5):				
Biparametric MRI PI-RADS v2.1 score (1–5):				
RE-ASSESS, TAKING INTO ACCOUNT INFORMATION FROM DCE SEQUENCE (MPMRI):				
Multiparametric MRI Likert score (1–5):				
Multiparametric MRI PI-RADS v2.1 score (1–5):				
Target appearance (select one):	<input type="checkbox"/> Focal <input type="checkbox"/> Diffuse	<input type="checkbox"/> Focal <input type="checkbox"/> Diffuse	<input type="checkbox"/> Focal <input type="checkbox"/> Diffuse	<input type="checkbox"/> Focal <input type="checkbox"/> Diffuse
Biaxial diameter on sequence where it was largest, in axial plane (mm x mm):				
Sequence used to measure biaxial diameter (select one):	<input type="checkbox"/> T2 <input type="checkbox"/> High b <input type="checkbox"/> ADC <input type="checkbox"/> DCE	<input type="checkbox"/> T2 <input type="checkbox"/> High b <input type="checkbox"/> ADC <input type="checkbox"/> DCE	<input type="checkbox"/> T2 <input type="checkbox"/> High b <input type="checkbox"/> ADC <input type="checkbox"/> DCE	<input type="checkbox"/> T2 <input type="checkbox"/> High b <input type="checkbox"/> ADC <input type="checkbox"/> DCE

TRIAL IDENTIFIER:

PARTICIPANT INITIALS:

PART TWO: NEW DCE-TARGETS ON DYNAMIC CONTRAST ENHANCED SEQUENCE

*** Please note:** this is a **subjective decision** by the radiologist as to whether new parts of an existing lesion on bpMRI would need to be declared as a **new target** in order **not to be missed on biopsy**. A clear example of when to declare a new DCE-Target would be if the non-overlapping part of the lesion on DCE crosses into a new sector on the PI-RADSv2.1 sector diagram

5. Any new targets should be labelled **DCE-Target-x**.
 - a. The first new, most suspicious, target should be **DCE-Target-1**. The second if applicable, **DCE-Target-2** and so on.
6. A maximum of **4 new targets** can be drawn on this report (**Report 2**).
 - a. Thus, a maximum of **8 targets** can be drawn in total (4 carried over from **Report 1** and 4 new DCE targets).
7. **On the diagram on Page 2, every** lesion drawn must have the following marked and labelled:
 - a. Target number
 - b. bpMRI status (positive or negative)
 - c. mpMRI status (positive or negative)
 - d. Likert score for mpMRI
 - e. PI-RADS v2.1 score for mpMRI

e.g. DCE-Target-1. bpMRI negative. mpMRI positive. Likert 4. PI-RADS 2.
8. Then complete **Table 2** and the rest of the MRI proforma.

TRIAL IDENTIFIER:

PARTICIPANT INITIALS:

Table 2. Information from Targets identified **ONLY** by DCE, which were **not** identified on the **biparametric MRI** (if applicable). If there are no DCE-Targets then leave Table 2 blank & move onto overall patient Likert & PI-RADS scores):

TARGET SPECIFIC INFORMATION	DCE-TARGET 1	DCE-TARGET 2	DCE-TARGET 3	DCE-TARGET 4
DCE-Target (select if new lesion or part of existing lesion bigger on DCE):	<input type="checkbox"/> New <input type="checkbox"/> Existing	<input type="checkbox"/> New <input type="checkbox"/> Existing	<input type="checkbox"/> New <input type="checkbox"/> Existing	<input type="checkbox"/> New <input type="checkbox"/> Existing
Location of suspicious area(s) (select one):	<input type="checkbox"/> Right <input type="checkbox"/> Left <input type="checkbox"/> Bilateral	<input type="checkbox"/> Right <input type="checkbox"/> Left <input type="checkbox"/> Bilateral	<input type="checkbox"/> Right <input type="checkbox"/> Left <input type="checkbox"/> Bilateral	<input type="checkbox"/> Right <input type="checkbox"/> Left <input type="checkbox"/> Bilateral
Location in prostate according to PI-RADS v2.1 41-sector diagram (select the one main location which contains the target):	<input type="checkbox"/> Base <input type="checkbox"/> Mid <input type="checkbox"/> Apex <input type="checkbox"/> Seminal Vesicle	<input type="checkbox"/> Base <input type="checkbox"/> Mid <input type="checkbox"/> Apex <input type="checkbox"/> Seminal Vesicle	<input type="checkbox"/> Base <input type="checkbox"/> Mid <input type="checkbox"/> Apex <input type="checkbox"/> Seminal Vesicle	<input type="checkbox"/> Base <input type="checkbox"/> Mid <input type="checkbox"/> Apex <input type="checkbox"/> Seminal Vesicle
Main sector which contains the lesion according to PI-RADS v2.1 41-sector diagram (write one , e.g. "PZpl"):				
Multiparametric MRI Likert score (1–5):				
Multiparametric MRI PI-RADS v2.1 score (1–5):				
Target appearance (select one):	<input type="checkbox"/> Focal <input type="checkbox"/> Diffuse	<input type="checkbox"/> Focal <input type="checkbox"/> Diffuse	<input type="checkbox"/> Focal <input type="checkbox"/> Diffuse	<input type="checkbox"/> Focal <input type="checkbox"/> Diffuse
Biaxial diameter on dominant sequence in axial plane (mm x mm):				
Looking back again at the T2W and DWI only , is the DCE-target identified here actually visible on the bpMRI?	<input type="checkbox"/> No <input type="checkbox"/> Yes	<input type="checkbox"/> No <input type="checkbox"/> Yes	<input type="checkbox"/> No <input type="checkbox"/> Yes	<input type="checkbox"/> No <input type="checkbox"/> Yes
If you answered Yes , please specify whether the lesion was missed on 1 st look or whether it was seen but scored a 1 or 2 on PI-RADS v2.1 and Likert	<input type="checkbox"/> Missed on 1 st look <input type="checkbox"/> Seen on 1 st look but scored a 1 or 2	<input type="checkbox"/> Missed on 1 st look <input type="checkbox"/> Seen on 1 st look but scored a 1 or 2	<input type="checkbox"/> Missed on 1 st look <input type="checkbox"/> Seen on 1 st look but scored a 1 or 2	<input type="checkbox"/> Missed on 1 st look <input type="checkbox"/> Seen on 1 st look but scored a 1 or 2

TRIAL IDENTIFIER:

PARTICIPANT INITIALS:

Please complete the **overall scores** regardless of whether there are any Targets identified above:

<p>Overall patient Likert score</p> <p>Enter the highest Likert score on either biparametric MRI or multiparametric MRI</p>		<p>Overall patient PI-RADS v2.1 score</p> <p>Enter the highest PI-RADS v2.1 score on either biparametric MRI or multiparametric MRI</p>	
---	--	---	--

Please note: if a lesion was suspicious on biparametric MRI but **not** suspicious on mpMRI (i.e. bpMRI +ve, mpMRI -ve), it should still be biopsied if either the Likert or PI-RADS v2.1 score on bpMRI is ≥ 3 . This highest score on either bpMRI or mpMRI should be entered above.

Table 3. Staging information. Complete **only** if a Target has been identified above. Select **one option** each time:

Radiological stage:	<input type="checkbox"/> T2a <input type="checkbox"/> T2b <input type="checkbox"/> T2c <input type="checkbox"/> T3a <input type="checkbox"/> T3b <input type="checkbox"/> T4 Radiological T3a = unequivocal extracapsular disease
Likelihood of right -sided extracapsular spread *: 1 = highly unlikely , 3 = equivocal, 5 = highly likely	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5
Likelihood of left -sided extracapsular spread *:	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5
Capsular involvement on DCE :	<input type="checkbox"/> No <input type="checkbox"/> Yes, on right <input type="checkbox"/> Yes, on left <input type="checkbox"/> Yes, on both sides
Likelihood of right seminal vesicle involvement:	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5
Likelihood of left seminal vesicle involvement:	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5
Seminal vesicle involvement on DCE :	<input type="checkbox"/> No <input type="checkbox"/> Yes, on right <input type="checkbox"/> Yes, on left <input type="checkbox"/> Yes, on both sides
Likelihood of urethral sphincter involvement:	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5
Urethral sphincter involvement on DCE :	<input type="checkbox"/> No <input type="checkbox"/> Yes, on right <input type="checkbox"/> Yes, on left <input type="checkbox"/> Yes, on both sides
Likelihood of bladder neck involvement:	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5
Bladder neck involvement on DCE :	<input type="checkbox"/> No <input type="checkbox"/> Yes
Likelihood of rectal involvement:	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5
Rectal wall involvement on DCE :	<input type="checkbox"/> No <input type="checkbox"/> Yes

* See PI-RADS v2.1 guidelines for examples of features suggestive of extracapsular spread.

TRIAL IDENTIFIER:

PARTICIPANT INITIALS:

MRI Quality. Please **complete** this for all MRIs regardless of whether a Target was identified:

Was there a problem with the quality of the DCE sequence?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
If problems with DCE, please specify: Tick all that apply	<input type="checkbox"/> Rectal air	<input type="checkbox"/> Movement artefact
	<input type="checkbox"/> Prosthesis	<input type="checkbox"/> Other
If other, please describe:		
Was the quality of the scan sufficient for you to make a diagnostic assessment?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Based on the quality of the mpMRI scan and your typical practice, would you recommend a repeat multiparametric MRI be performed?	<input type="checkbox"/> Yes	<input type="checkbox"/> No

Biopsy protocol guidelinesIt is **mandatory** to follow these recommendations below:

Number of MRI targets	Location of MRI targets in prostate	Number of MRI-targeted biopsy cores	Number of contralateral systematic cores	Total number of biopsy cores
0	If PSA Density is < 0.15ng/ml/ml			0
0	If PSA Density is ≥ 0.15ng/ml/ml, then 12 systematic biopsy cores are taken (6 from each side)			12
1	Unilateral	4	6	10
2	Unilateral	8	6	14
3	Unilateral	12	6	18
4–8	Unilateral	16–32	6	22–38
1	Bilateral (<i>e.g.</i> crossing midline)	4	0	4
2	Bilateral	8	0	8
3	Bilateral	12	0	12
4–8	Bilateral	16–32	0	16–32

Note: For 4–8 MRI targets, determine the number of MRI-targeted cores by using the principle of 4 cores per MRI target.

TRIAL IDENTIFIER:

PARTICIPANT INITIALS:

Recommended Biopsy Plan for biopsy operator to follow

The radiologist should now complete this biopsy plan which should be passed directly to the person performing biopsy (if one is required) along with the labelled diagram on Page 2:

Even if radiologists do not typically write biopsy plans, we request they do this here following the protocol in the table above, in order to reduce errors between linking the MRI information to the protocol biopsy plan.

Number of MRI-targets to biopsy with MRI-targeted biopsy: <i>(Note: Targets which are only suspicious on bpMRI should still be biopsied. The number of MRI-targets for biopsy therefore includes MRI targets identified only on bpMRI, only on mpMRI or on both bpMRI and mpMRI and on either the Likert scoring system or the PIRADsv2.1 scoring system)</i>	
Total number of MRI-targeted biopsy cores to be taken: <i>(Note: 4 biopsy cores should be taken per lesion)</i>	
Total number of systematic biopsy cores to be taken: <i>(Note: Systematic cores should be peripheral zone-focused cores)</i>	
Number of systematic cores to be taken from right side of prostate: <i>(Note: do not take systematic cores from the same side as an MRI target)</i>	
Number of systematic cores to be taken from left side of prostate: <i>(Note: do not take systematic cores from the same side as an MRI target)</i>	
Total number of systematic and targeted cores to be taken	

Radiologist (Forename, Surname):		Date:	
-------------------------------------	--	-------	--



Supplementary Appendix 2: Detailed PRIME Biopsy Plans

To be pragmatic and allow results to be generalisable to biopsy practice around the world, biopsies can be performed transperineally (**Figures 1 and 2**) or transrectally (**Figures 3 and 4**) as per local practice. We split this Appendix into these sections, respectively.

If there is an MRI lesion (scores 3, 4 or 5 on *either* Likert or PI-RADS v2.1 scoring systems), then MRI-targeted biopsy and some limited contralateral systematic biopsy should be performed. MRI-targeted biopsy should be performed **first**, with 4 cores per suspicious area. Then the systematic biopsy cores should be taken but avoid taking biopsies from the same side of the prostate that targeted biopsies were taken from.

Table of Contents

Systematic Transperineal Biopsy Schema.....	2
Non-suspicious MRI but a PSA Density of $\geq 0.15\text{ng/mL/mL}$ scenario.....	2
Suspicious MRI lesion scenarios.....	4
<i>Single lesion scenario</i>	4
<i>Bilateral lesions scenario</i>	4
<i>Lesion crossing midline scenario</i>	5
<i>Bilateral diffuse change on Likert scoring scenario</i>	5
<i>New lesion is revealed on DCE sequence scenario</i>	6
<i>New part of existing lesion is revealed on DCE sequence scenario</i>	6
Systematic Transrectal Biopsy Schema.....	7
Non-suspicious MRI but a PSA Density of $\geq 0.15\text{ng/mL/mL}$ scenario.....	7
Suspicious MRI lesion scenarios.....	9
<i>Single lesion scenario</i>	9
<i>Bilateral lesions scenario</i>	10
<i>Lesion crossing midline scenario</i>	11
<i>Bilateral diffuse change on Likert scoring scenario</i>	12
<i>New lesion is revealed on DCE sequence scenario</i>	13
<i>New part of existing lesion is revealed on DCE sequence scenario</i>	14
Summary Biopsy Guidelines.....	16

Systematic Transperineal Biopsy Schema

Figures 1 and **2A-F** depict examples of how to perform the systematic biopsy in the **absence** of an MRI lesion and in the **presence** of MRI lesions, respectively.

Non-suspicious MRI but a PSA Density of $\geq 0.15\text{ng/mL/mL}$ scenario

In patients with a **non-suspicious MRI but a PSA Density of $\geq 0.15\text{ng/mL/mL}$** , 12-core systematic biopsy should be performed (**Figure 1**).

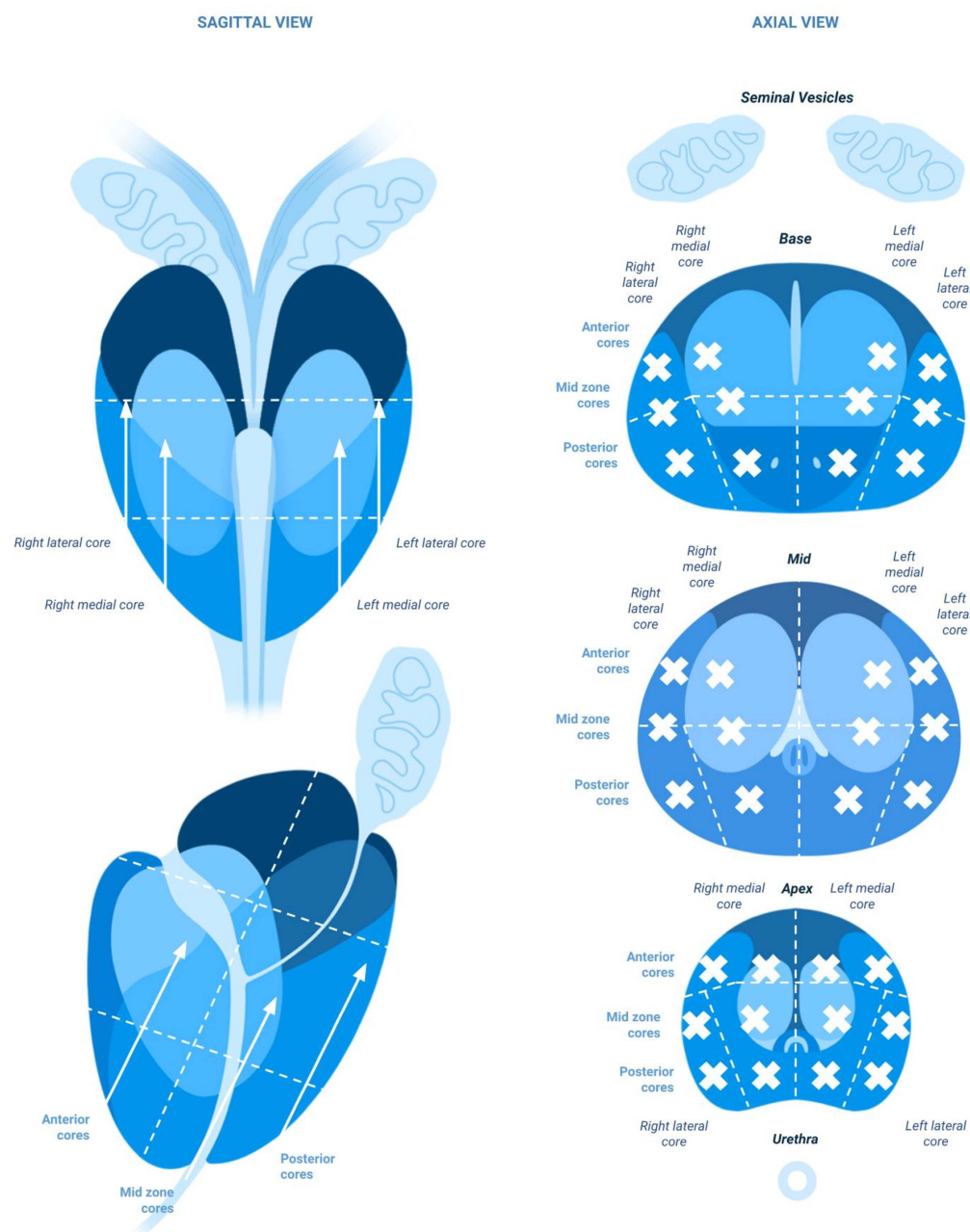
The number of systematic cores that should be taken per patient is **12**.

Systematic biopsy cores are taken from:

- Right anterior zone (2 cores)
- Right mid zone (2 cores)
- Right posterior zone (2 cores)
- Left anterior zone (2 cores)
- Left mid zone (2 cores)
- Left posterior zone (2 cores)

Systematic biopsy cores should be stored and labelled in a way that their **location** can be identified when the pathologist reports the result.

Figure 1. The transperineal biopsy schema for men with a **non-suspicious MRI** (scores 1 or 2 on both Likert and PI-RADS v2.1 scoring systems) *but* a PSA Density of $\geq 0.15\text{ng/mL/mL}$, undergoing 12-core systematic biopsy.

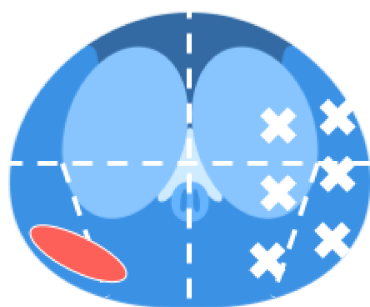


For each pair of biopsies – one core is more lateral, one core is more medial. From anterior—posterior, there are 3 planned rows of biopsies – anterior, mid zone, posterior. Avoid biopsy around the urethra.

Suspicious MRI lesion scenarios

Figure 2. Examples of how to perform transperineal biopsies in patients with an MRI Target (scores 3, 4 or 5 on *either* Likert or PI-RADS v2.1 scoring systems).

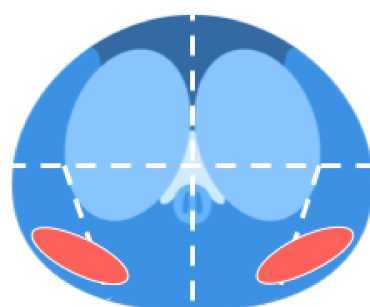
2A. Single lesion example.



This is a single lesion in the right mid-gland peripheral zone posteromedially (PZ pm) and posterolaterally (PZ pl).

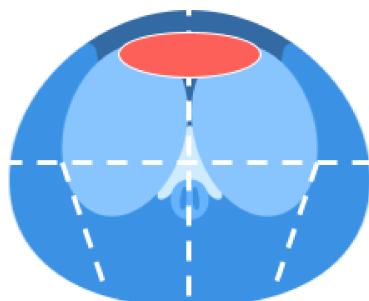
- Take **4 targeted biopsies** from the Target.
- Then take **6 peripheral zone focused biopsies** from the **contralateral** side.
- Do **not** resample the targeted biopsy side.

2B. Bilateral peripheral zone lesions example.



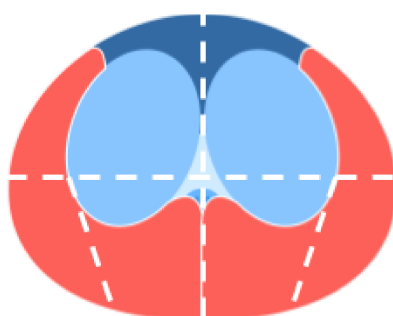
There are **two lesions**: one in right mid-gland, peripheral zone posteromedially and posterolaterally (PZ pm and PZ pl); one in left mid-gland, peripheral zone posteromedially and posterolaterally (PZ pm and PZ pl).

- Take **4 targeted biopsies** from *each* Target – *i.e.* **8 targeted biopsies** in **total**.
- **Do not take any systematic biopsies** as targeted biopsies are taken from both sides of the prostate.

2C. Lesion crossing midline example.

This is one lesion crossing the midline in the mid-gland, anterior fibromuscular stroma.

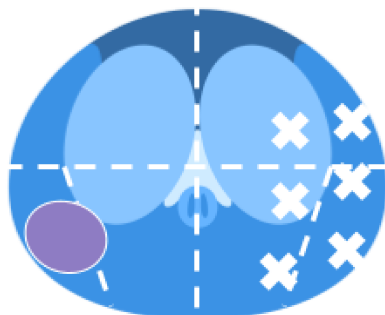
- Take **4 targeted biopsies** from the Target.
- **Do not take any systematic biopsies** as targeted biopsies are taken from both sides of the prostate.

2D. Bilateral diffuse change on Likert scoring example.

In the circumstance where on Likert scoring, the peripheral zone gives diffuse change, scoring 3 out of 5, arbitrarily **treat each peripheral zone** as a **different Target**.

- Take **4 targeted biopsies** from *each half* of the peripheral zone – *i.e. 8 biopsies* in total.
- **Do not take any systematic biopsies** as targeted biopsies are taken from both sides of the prostate.

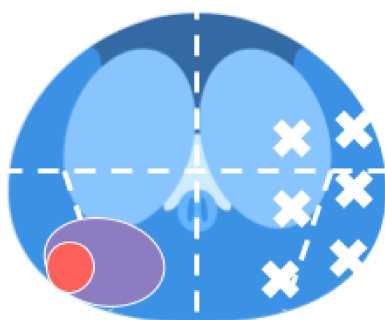
2E. A new lesion is revealed on DCE sequence example.



This is one lesion in the right mid-gland, peripheral zone posterolaterally. This **new Target** was specifically *not* suspicious (scored 1 or 2 on both Likert and PI-RADS v2.1) on bpMRI sequences (T2W and DWI). However, when the contrast sequence is revealed, the lesion appears to be suspicious (scored 3, 4 or 5 on Likert) on the dynamic contrast-enhanced (DCE) sequence than on the bpMRI.

- Thus, label the **new lesion** as a **DCE-Target**.
- Take **4 targeted biopsies** from **DCE-Target-1**.
- Then take **6 peripheral zone focused biopsies** from the **contralateral** side of the prostate.
- Do **not** resample the targeted biopsy side.

2F. A new **part** of an *existing* lesion is revealed on DCE sequence example.



There are two lesions in this example. **Target 1 (red)** was suspicious on **both** bpMRI and mpMRI. It is in the right mid-gland, peripheral zone, posterolaterally (PZ pl). It scores Likert 4 and PI-RADS v2.1 4.

However, when the contrast sequence is revealed, this lesion appears to be larger on the DCE sequence than on bpMRI. The part of the lesion that is **non-overlapping** would **not** have been

target biopsied if bpMRI alone was used. Thus, the second lesion (the non-overlapping part, **purple**) is called **DCE Target 1**. It is in the right mid-gland, peripheral zone, posteromedially (PZ pm).

Thus, the instructions are as follows in this instance:

- Take **4 targeted biopsies** from **Target 1**.
- Take **4 targeted biopsies** from **DCE Target 1**.
- Take **6 peripheral zone focused biopsies** from the **contralateral** side of the prostate.
- Do **not** resample the targeted biopsy side.

Systematic Transrectal Biopsy Schema

Figures 3 and **4** depict examples of how to perform the systematic biopsy in the **absence** of an MRI lesion and in the **presence** of MRI lesions, respectively.

Non-suspicious MRI but a PSA Density of $\geq 0.15\text{ng/mL/mL}$ scenario

In patients with a **non-suspicious MRI but a PSA Density of $\geq 0.15\text{ng/mL/mL}$** , 12-core systematic biopsy should be performed (**Figure 3**).

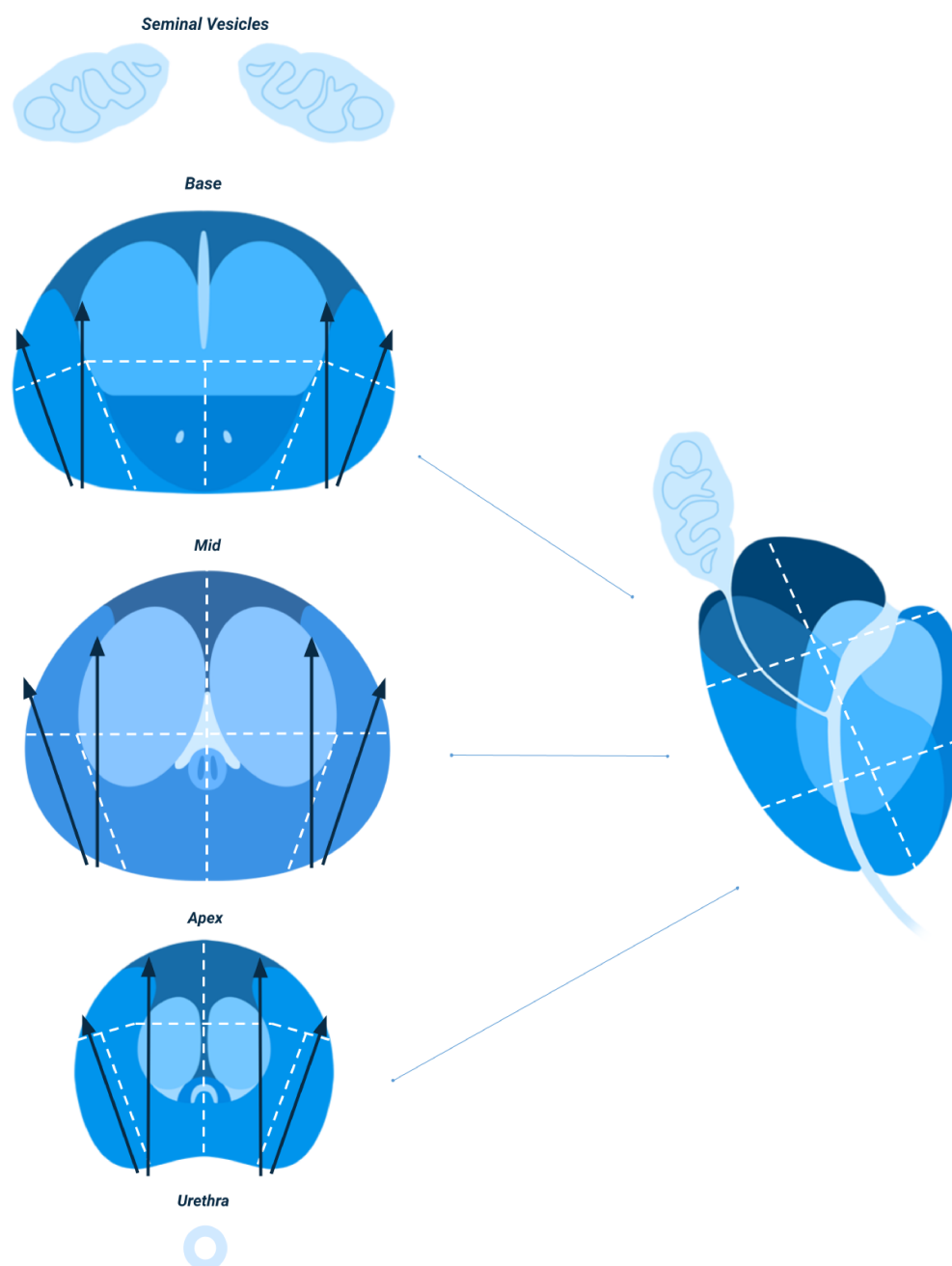
If performing biopsies transrectally, systematic biopsy cores should be taken from:

- Right base (2 cores)
- Right mid gland (2 cores)
- Right apex (2 cores)
- Left base (2 cores)
- Left mid gland (2 cores)
- Left apex (2 cores)

Systematic biopsy cores should be stored and labelled in a way that their location can be identified when the pathologist reports the result.

The 12 systematic biopsies **should be focused on the peripheral zone**. The urethra should be avoided.

Figure 3. The transrectal biopsy schema for men with a **non-suspicious MRI** (scores 1 or 2 on both Likert and PI-RADS v2.1 scoring systems) *but* a PSA Density of $\geq 0.15\text{ng/mL/mL}$, undergoing 12-core systematic biopsy.



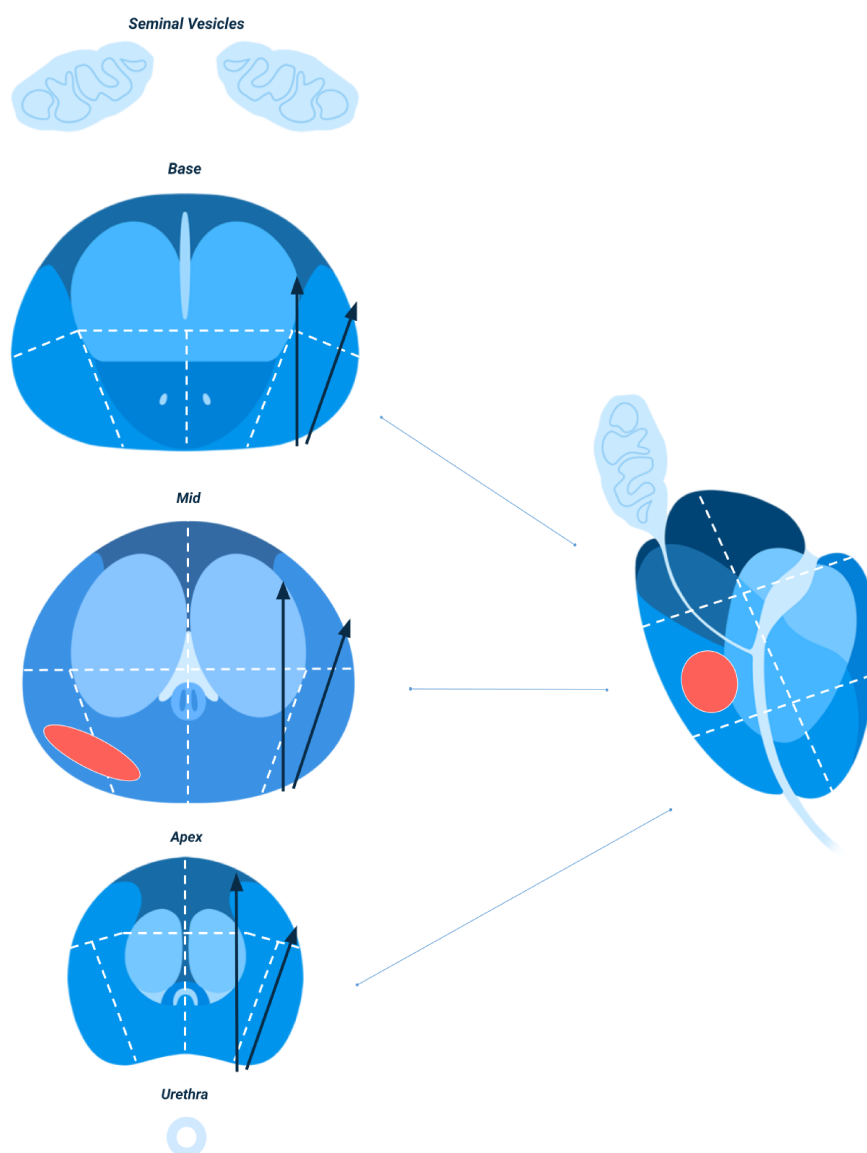
Designed by Aqua Asif



Suspicious MRI lesion scenarios

Figure 4. Examples of how to perform transrectal biopsies in patients with an MRI Target (scores 3, 4 or 5 on *either* Likert or PI-RADS v2.1 scoring systems).

4A. Single lesion example.



This is a single lesion in the right mid-gland peripheral zone posteromedially (PZ pm) and posterolaterally (PZ pl).

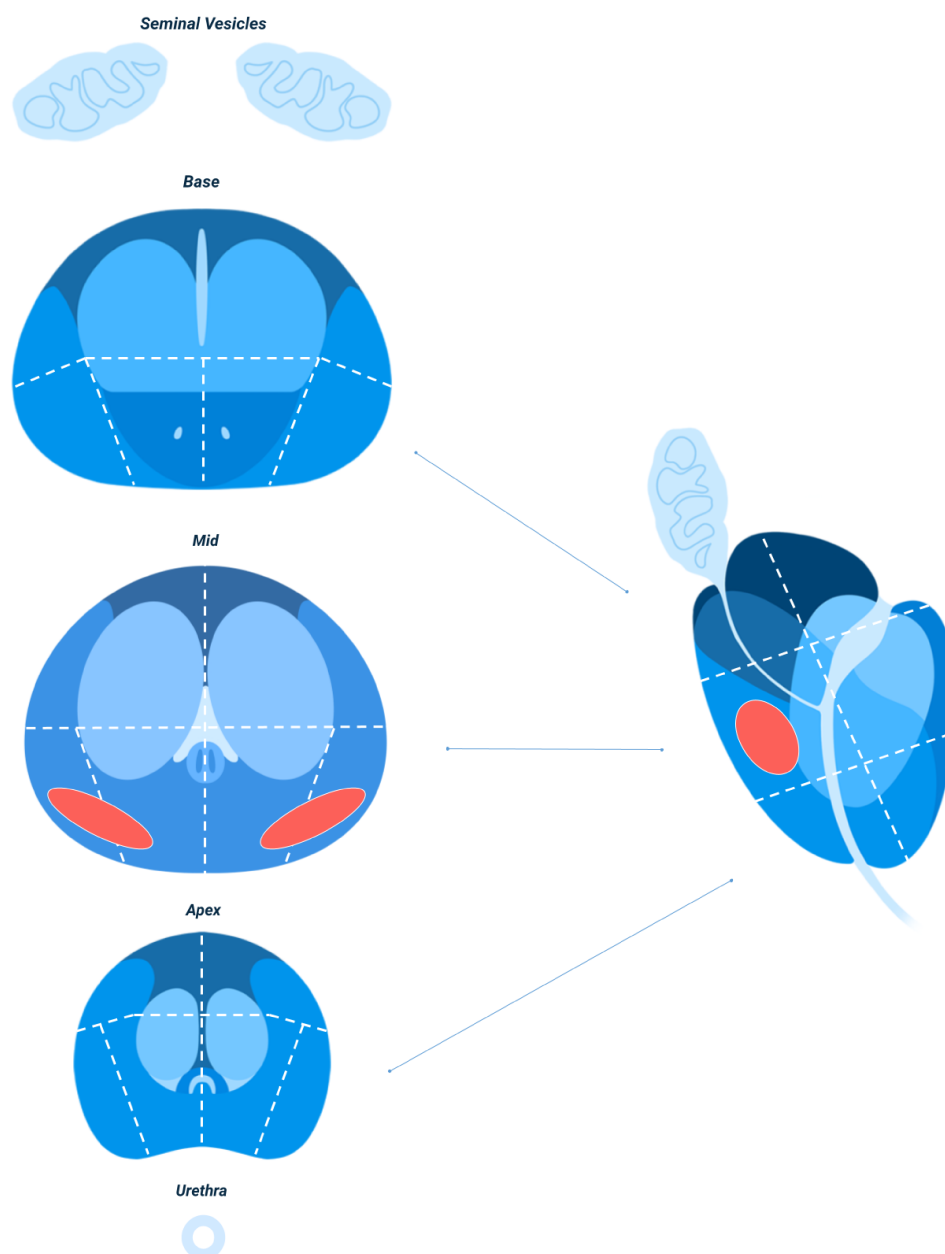
- Take **4 targeted biopsies** from the Target.
- Then take **6 peripheral zone focused biopsies** from the **contralateral** side.

Designed by Aqua Asif



- Do **not** resample the targeted biopsy side.

4B. Bilateral peripheral zone lesions example.

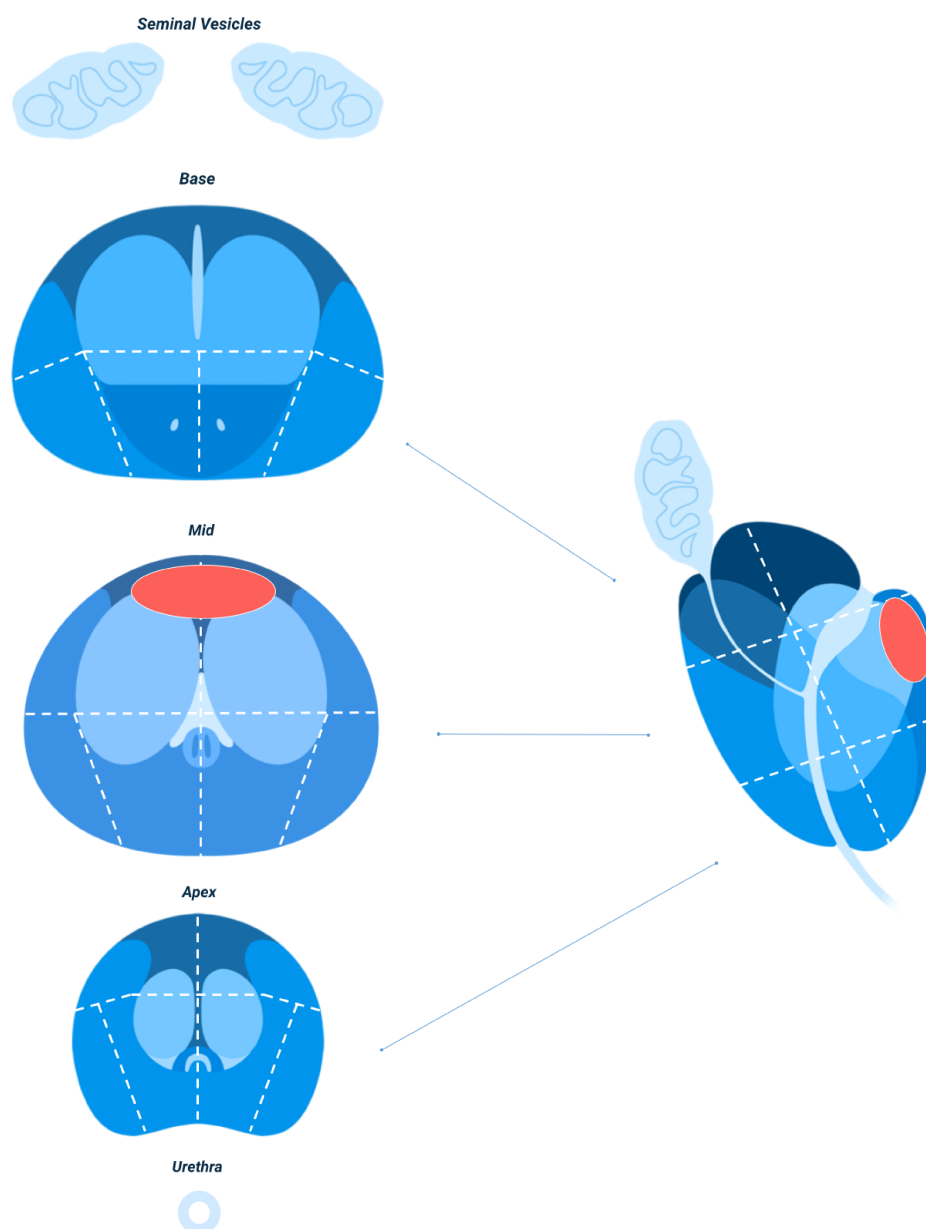


There are **two lesions**: one in right mid-gland, peripheral zone posteromedially and posterolaterally (PZ pm and PZ pl); one in left mid-gland, peripheral zone posteromedially and posterolaterally (PZ pm and PZ pl).

- Take **4 targeted biopsies** from **each** Target – *i.e.* **8 targeted biopsies** in **total**.

- **Do not take any systematic biopsies** as targeted biopsies are taken from both sides of the prostate.

4C. Lesion crossing midline example.

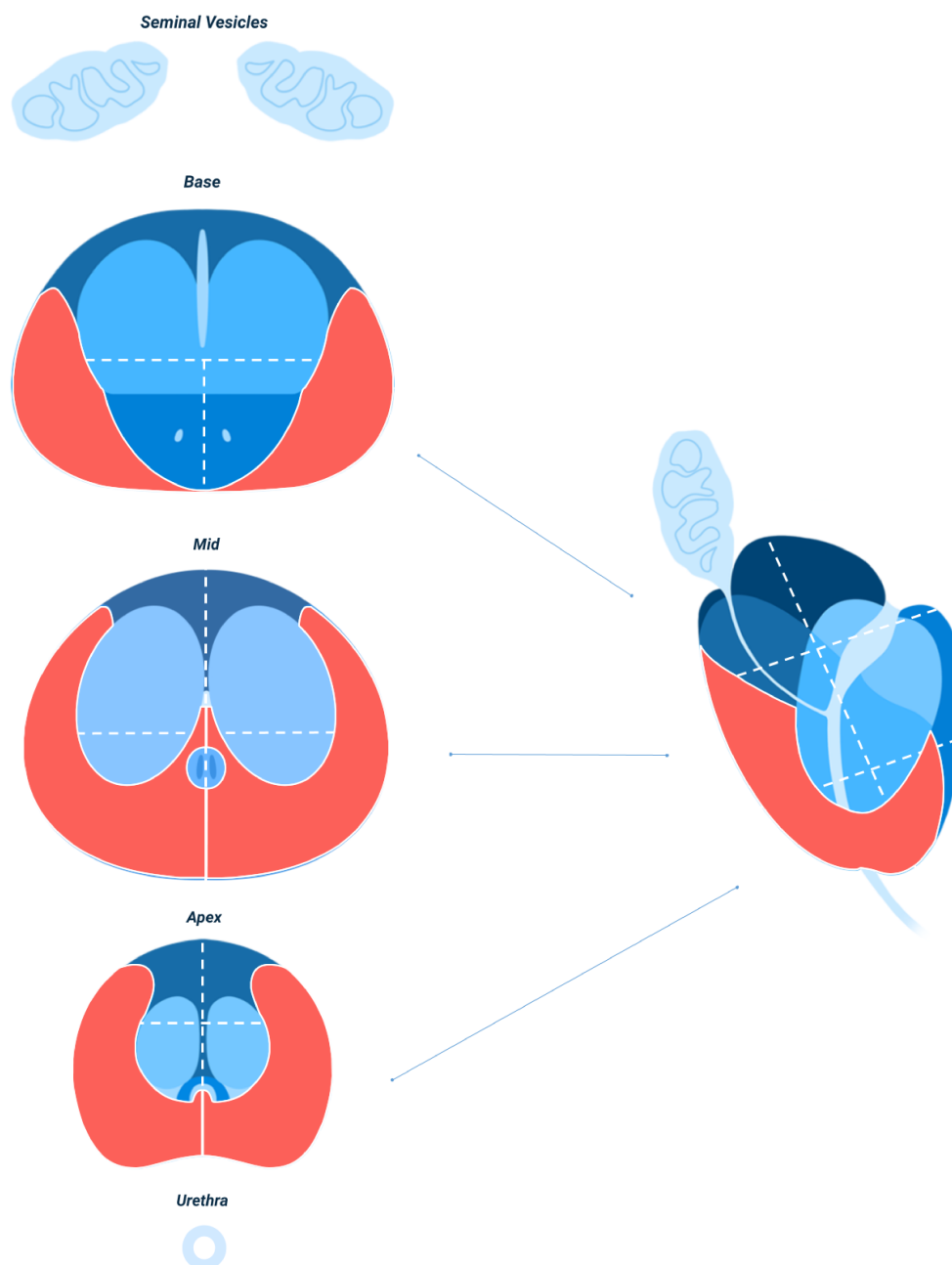


This is one lesion crossing the midline in the mid-gland, anterior fibromuscular stroma.

- Take **4 targeted biopsies** from the Target.

- **Do not take any systematic biopsies** as targeted biopsies are taken from both sides of the prostate.

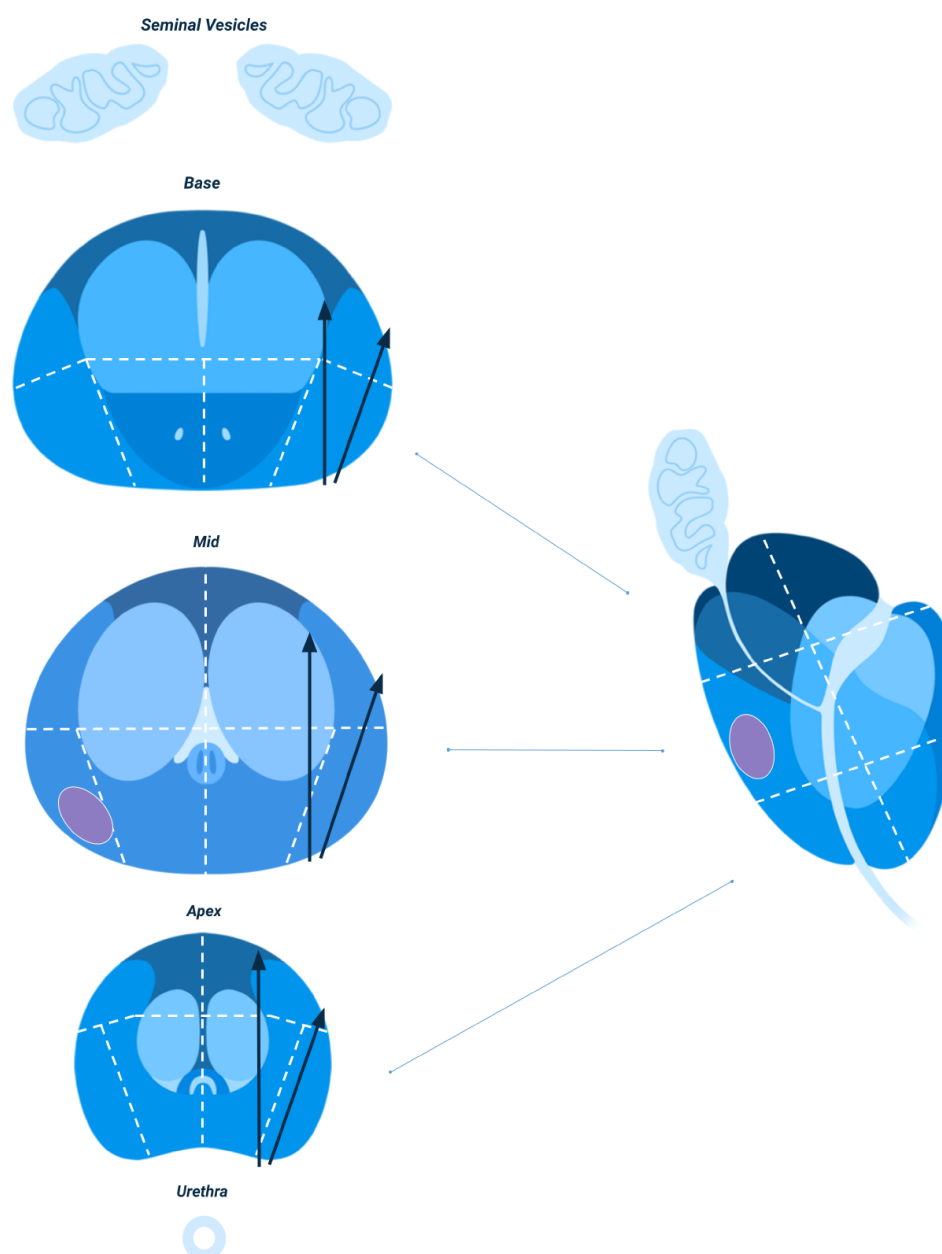
4D. Bilateral diffuse change on Likert scoring example.



In the circumstance where on Likert scoring, the peripheral zone gives diffuse change, scoring 3 out of 5, arbitrarily **treat each peripheral zone as a different Target**.

- Take **4 targeted biopsies** from *each half* of the peripheral zone – *i.e.* **8 biopsies** in total.
- **Do not take any systematic biopsies** as targeted biopsies are taken from both sides of the prostate.

4E. A new lesion is revealed on DCE sequence example.



This is one lesion in the right mid-gland, peripheral zone posterolaterally. This **new Target** was specifically *not* suspicious (scored 1 or 2 on both Likert and PI-RADS v2.1) on bpMRI sequences (T2W and DWI). However, when the contrast sequence is revealed, the lesion

appears to be suspicious (scored 3, 4 or 5 on Likert) on the dynamic contrast-enhanced (DCE) sequence than on the bpMRI.

- Thus, label the **new lesion** as a **DCE-Target**.
- Take **4 targeted biopsies** from **DCE-Target-1**.
- Then take **6 peripheral zone focused biopsies** from the **contralateral** side of the prostate.
- Do **not** resample the targeted biopsy side.

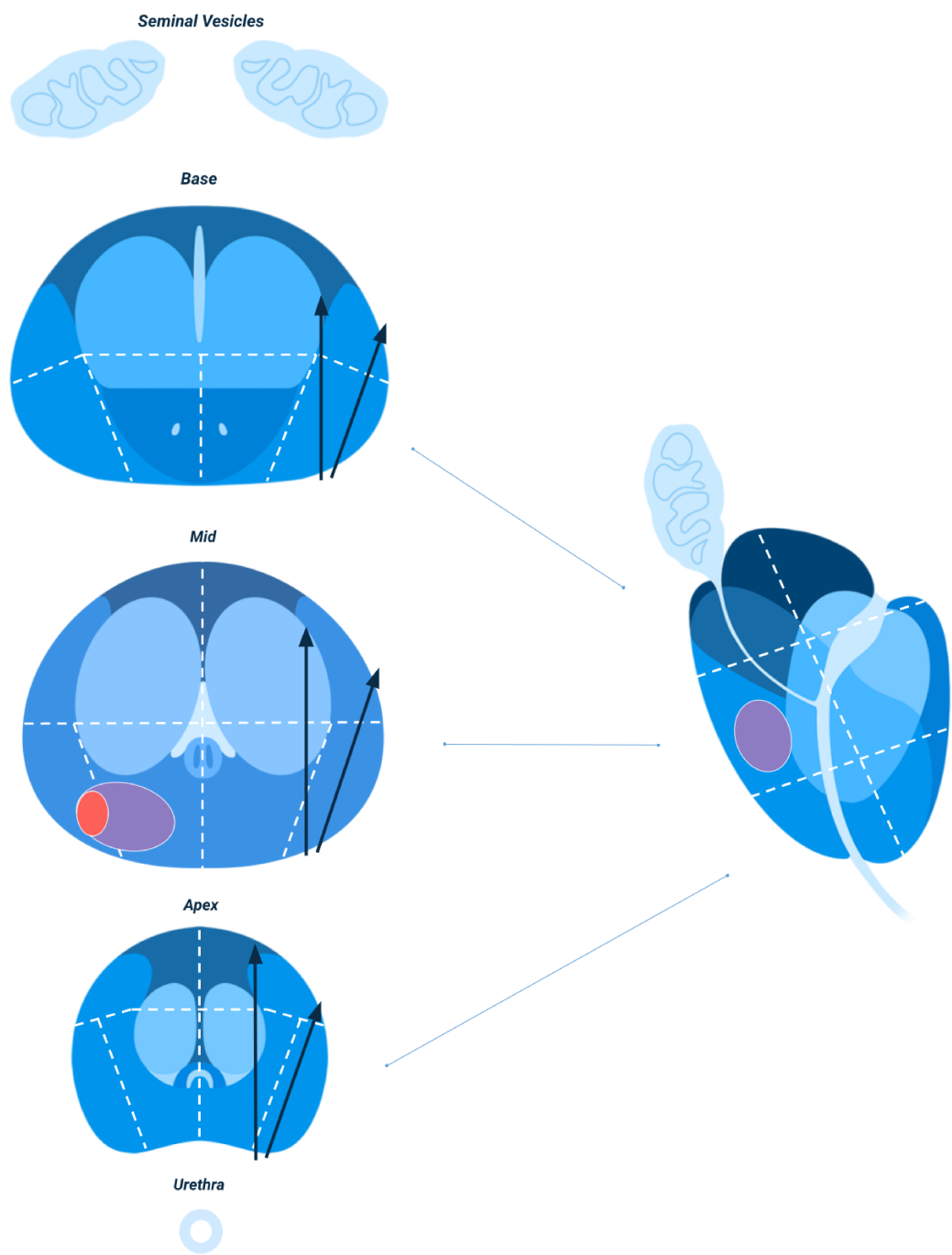
4F. A new **part** of an *existing* lesion is revealed on DCE sequence example.

There are two lesions in this example. **Target 1 (red)** was suspicious on **both** bpMRI and mpMRI. It is in the right mid-gland, peripheral zone, posterolaterally (PZ pl). It scores Likert 4 and PI-RADS v2.1 4.

However, when the contrast sequence is revealed, this lesion appears to be larger on the DCE sequence than on bpMRI. The part of the lesion that is **non-overlapping** would **not** have been target biopsied if bpMRI alone was used. Thus, the second lesion (the non-overlapping part, **purple**) is called **DCE Target 1**. It is in the right mid-gland, peripheral zone, posteromedially (PZ pm).

Thus, the instructions are as follows in this instance:

- Take **4 targeted biopsies** from **Target 1**.
- Take **4 targeted biopsies** from **DCE Target 1**.
- Take **6 peripheral zone focused biopsies** from the **contralateral** side of the prostate.
- Do **not** resample the targeted biopsy side.



Designed by Aqua Asif



Summary Biopsy Guidelines

Number of MRI targets	Location of MRI targets in prostate	Number of MRI-targeted biopsy cores	Number of contralateral systematic cores	Total number of biopsy cores
0	If PSA Density is < 0.15ng/ml/ml			0
0	If PSA Density is \geq 0.15ng/ml/ml, then 12 systematic biopsy cores are taken (6 from each side)			12
1	Unilateral	4	6	10
2	Unilateral	8	6	14
3	Unilateral	12	6	18
4–8	Unilateral	16–32	6	22–38
1	Bilateral (e.g. crossing midline)	4	0	4
2	Bilateral	8	0	8
3	Bilateral	12	0	12
4–8	Bilateral	16–32	0	16–32

Please present on local headed paper

REC Number:
IRAS Number: 282789

Subject Identification: _____
Study Number ; _____

CONSENT FORM

Title of Project: PRostate Imaging using MRI +/- contrast Enhancement (PRIME)

Name of Researcher:

Please initial box

1. I confirm that I have read and understand the information sheet dated..... (version.....) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from the sponsor of the trial (University College London), responsible persons authorised by the sponsor, from regulatory authorities, from the NHS Trust and from PRIME study researchers who may be outside of my local centre, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
4. I agree to my GP being informed of my participation in the study. ☐
5. I give my permission for the PRIME research team at my local centre to hold identifiable information such as my name, address, date of birth, email address, mobile phone number, NHS number or other applicable hospital identifier. I understand this may be used to collect longer term healthcare information on me from national records, such as the Office for National Statistics, NHS Digital, Public Health England, and other applicable NHS information systems, or other relevant national databases. This data may be linked to my data from the PRIME study in future research. ☐

IRAS Reference Number 282789
PRIME Consent Form Version 2.0 Dated 27APR2021

6. I give permission to be contacted for further information in the future. This may include requests to complete quality of life questionnaires or for ascertaining future health status, if required. ☐

7. I give permission for my samples to be sent to UCL by courier for quality control assessments. ☐

8. I give permission for my anonymized data to be used for teaching and educational purposes for healthcare professionals. ☐

9. I give my permission for my anonymized data to be shared with affiliated researchers and commercial partners who are approved by the PRIME study team for future research if deemed suitable by the PRIME Chief Investigator ☐

10. I give my permission to be approached for other studies in the future that may be relevant to me, and for my study data collected in PRIME to be used for this purpose. ☐

11. I agree to take part in the above study and to complete study procedures outlined in the patient information sheet provided. ☐

All boxes above must be initialed for consent to be valid

Name of Participant

Date

Signature

Name of Person
taking consent

Date

Signature

When completed: 1 for participant; 1 (original) for researcher site file; 1 to be kept in medical notes.

PLACE HOSPITAL LETTER HEAD ON FIRST PAGE ONLY.

Affix patient sticker / details here

Version 3.0 8 June 2021

**This is the Patient Information Sheet for a Health Research Study called
PRIME**

Study Short Title: Prostate Imaging using MRI +/- contrast Enhancement

Study acronym: **PRIME**

Chief Investigator: Mr Veeru Kasivisvanathan

UCL Reference number: 135819

REC Reference number: 21/WM/0091

IRAS Number: 282789

We would like to invite you to take part in our research study. Before you decide we would like you to understand why you are being invited, why the research is being done and what it would involve for you. One of our team will go through the information sheet with you and answer any questions you have. Talk to others about the study if you wish.

Part 1 tells you the purpose of this study and what will happen to you if you take part. Part 2 gives you more detailed information about the conduct of the study.

Ask us if there is anything that is not clear. Please take as much time as you need to consider the study.

Part 1

1. Why have I been invited?

You are being invited because you may require further investigation of your prostate with an MRI scan and / or a prostate biopsy. You have not been diagnosed with cancer but an MRI and / or a biopsy may be required to establish whether you do or do not have cancer. The clinical Urology team that you have been referred to has informed us that you may be eligible for this study.

2. What is the purpose of the study?

The standard way of diagnosing prostate cancer is to carry out a multiparametric prostate MRI scan and prostate biopsy. This type of MRI scan normally involves an injection of contrast into one of your veins.

Another type of MRI scan (biparametric) can be performed that does not require contrast, and therefore does not require the insertion of a cannula. We currently do not know for certain whether using this type of MRI will allow us to detect the same, more or less prostate cancer than if we use the standard (multiparametric) type of MRI. Current evidence supports the idea that using biparametric MRI may detect a similar amount of cancer to when it is not used but one advantage is it may allow a man to have a scan without contrast.

The main purpose of this study is to assess if biparametric MRI can provide similar information to multiparametric MRI. You will undergo a multiparametric MRI with a contrast injection, which is the typical method used for investigating the prostate for the presence of cancer. The doctor reviewing your scan will be asked to review the MRI scan in a particular order so that they can tell whether the additional information given by the contrast injection helps identifies prostate cancer.

If there is a suspicious area in the prostate on the MRI, a few biopsies can be directed at where the suspicious area is thought to be, also using an ultrasound probe in the back passage. If there is no suspicious area on the MRI and if you are at low risk of harbouring cancer, which occurs in about 30% of men, then no biopsy will be taken at all.

3. Do I have to take part?

It is up to you to decide to join the study. We will describe the study and go through this information sheet. If you agree to take part, we will then ask you to sign a consent form. You are free to withdraw at any time without giving a reason. This will not affect the standard of care you receive.

4. What are the benefits to me of taking part in this study?

The healthcare team carrying out the tests in the study are experienced in carrying out and interpreting these tests. The research team will ensure your tests are carried out as quickly as possible and will be a point of contact for you should you have any concerns or questions.

The information we get from this study will help improve the diagnosis of prostate cancer for men in the future.

5. What type of study is this?

This is a study evaluating the accuracy of diagnostic tests. In this trial, you will have the same investigation (multiparametric MRI) as your hospital normally does to investigate the prostate, but the doctor interpreting your scan will be asked to report this in a particular order. The full information will be available to the doctors as it would normally be available if you were not taking part in the study.

You will be required to attend a screening visit with a member of the research team who will spend around 40 minutes explaining what is involved in the study and making sure you are

eligible for the study. Where possible, all study visits that do not require a journey to the hospital will be performed remotely (e.g. over the phone or video call).

6. What will happen to me if I take part?

After you have attended the screening visit, if you are eligible to take part in the study, you will be asked to visit the hospital 2-3 times in total, which is the same as if you were not taking part in the study. After you consent to participating in the study, you will be asked to complete two short questionnaires which will ask about any symptoms related to your prostate that you may be having. These are questionnaires that are typically used as part of routine care. You would only undergo tests that you would normally have as part of routine care if you were not taking part in the study.

If you have not already had a prostate MRI, you will have one within a few weeks after the screening visit. The MRI takes about 40 minutes. Alternatively, it is possible that you are approached for the study after you have had your prostate MRI.

If you have an MRI with a high enough suspicion (MRI Score 3, 4 or 5) you will be booked for a biopsy following the MRI. If the MRI is non-suspicious but you are at high risk of having cancer because of a blood test result, (called your prostate specific antigen density) you will also undergo a prostate biopsy. If you do not need a biopsy (if your MRI is non-suspicious and your prostate specific antigen density is low) then you do not need to undergo a biopsy and we will explain this to you once your MRI results is available.

The biopsy procedure itself takes about 40 minutes and is typically carried out under local or general anaesthetic. Prostate biopsies, which take very small samples of prostate tissue, are taken from the prostate gland and sent to the lab to determine whether there is cancer there or not. If there is a suspicious area on the MRI scan, the MRI information will be used to influence where the biopsies are taken from. Software may be used to transfer additional information from the original MRI onto the screen when the biopsies are taken. In some centres, this would be exactly what you would normally get, and there would be no difference to standard of care. In other centres, their usual practice may be slightly different to this, and you may be required to have a few extra or fewer biopsies than what is typical in your usual centre. After the procedure, we then wait for the results and discuss treatment options with you in clinic at approximately 2-3 weeks after the biopsies.

Please note that the above time frames are suggested time frames and depending on clinical workload within the hospital, the time frame may be shorter or longer. This would be no different than if you were not part of the study.

Being involved in the study does not limit subsequent tests or treatment you may receive. If you do undergo further tests or treatment after the study is complete we may check the results of these on your records. We use the research data we have gathered from your involvement in the study to help us determine how good the diagnostic tests you have had are. We will work with other research teams to do this. We also ask your permission to use research data for teaching and education of other healthcare professionals. After completing the study, we also ask your permission to check your health through national databases. We may also contact you for further information in the future. This may include requests to complete quality of life questionnaires or for ascertaining future health status. All information which is collected about you during the course of the research will be kept strictly confidential, and any information about you which leaves the hospital will have your name and address removed so that you cannot be recognised. Please see Part 2 for further information on this.

7. What data will be collected and use of data

We will need to use information from your medical records for this research project. Your hospital will hold personal identifiable data on you. This information will include information such as age, PSA level, family history of medical conditions such as prostate cancer and examination findings. We allow the PRIME research team at your local site to hold

identifiable data on you, which will be for 10 years. Longer term data that may be requested from you include information on whether or not you have had further investigations or treatment for prostate problems and what the outcomes of those were as well as quality of life assessments. Non-identifiable data will be stored in the MARVIN database and the database will be transferred and stored at UCL within UCL's data safe haven. You will be given a subject number and a subject identifier, and this will be used on all your study records. The code for this number will be known to the investigators at your site so that the link between your name and the data we hold on the study database is not completely broken. Any paperwork for the study will be kept in locked cupboards, staff access to these cupboards is strictly controlled.

In general, UCL, as a university and a study sponsor, uses personally-identifiable information to conduct research to improve health, care and services. As a publicly-funded organisation, we have to ensure that it is in the public interest when we use personally-identifiable information from people who have agreed to take part in research. This means that when you agree to take part in a research study, we will use your data in the ways needed to conduct and analyse the research study. Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

Health and care research should serve the public interest, which means that we have to demonstrate that our research serves the interests of society as a whole. We do this by following the UK Policy Framework for Health and Social Care Research.

All data is managed in line with the Data Protection Act (2018) & General Data Protection Regulations (GDPR).

If you wish to raise a complaint on how we have handled your personal data, you can contact our Data Protection Officer who will investigate the matter. If you are not satisfied with our response or believe we are processing your personal data in a way that is not lawful you can complain to the Information Commissioner's Office (ICO).

UCL Data Protection Officer can be contacted on data-protection@ucl.ac.uk

8. What will I have to do?

You should attend your screening visit and if eligible for the study, await contact from the hospital for further dates of investigations. Unless otherwise advised by a doctor you should carry on with your normal activities and medication. Sometimes before a biopsy your doctor will prescribe you antibiotics and may ask you to stop blood-thinning medications.

You should undergo the necessary tests and biopsy procedures that you are advised to have by your doctor.

You should attend your follow up clinic appointment where we discuss your results. Treatment options will be discussed with you at the results clinic. In total you will typically be required to attend the hospital 2-3 times.

9. What are the alternatives for diagnosis?

An MRI scan and biopsies of the prostate if required are the standard ways in which prostate cancer is diagnosed.

10. What are the possible disadvantages and risks of taking part?

Being involved in the study is unlikely to expose you to additional risk than if you were not involved in the study but underwent the normal procedures for men referred for further investigation of prostate disease.

Risks of prostate biopsy include:

- Temporary discomfort in the back passage (most men)
- Blood in the urine – up to 2 weeks (most men)
- Blood in the semen – up to 3 months (most men)
- Blood in the back passage – up to 1 week (most men)
- Infection in the blood stream – 1-4 out of 100 men
- Urinary tract infection – 4 out of 100 men
- Urinary retention – 1 out of 100 men
- Adverse reaction to antibiotics – less than 1 in 100 men

Risks of MRI include:

- Discomfort from cannulation
- Allergic reaction:
 - Mild reaction e.g. rash, itching – less than 1 in 250 men
 - Moderate reaction e.g. nausea, omitting – less than 1 in 2000 men
 - Severe reaction e.g. breathing problems – less than 1 in 10000 men

In some centres, you would receive exactly what you would normally get outside of the study. In other centres, their usual practice may be slightly different to this, and you may be required to have a few extra or fewer biopsies than what is typical in your usual centre. However, there is no evidence that a few extra or fewer biopsies within the proposed study would result in additional adverse effects for you.

Before participating you should consider if this will affect any insurance you have and seek advice if necessary.

11. What should you do if you experience any problems during the study?

Though the risk is very low, if you do experience any possible signs of infection after biopsies (fevers and feeling generally unwell) then you should urgently go to your nearest accident and emergency department which is open 24 hours a day. If you are not able to pass urine you should urgently go to your nearest accident and emergency. If you are unsure about what to do or have any questions please call 0207 679 9092 between 9am and 5pm and a member of our team may be able to offer you advice or direct you to someone who can offer you advice.

If you experience any other untoward complication or need to see a doctor we would like to know about this so please let us know on the above number as soon as possible after the complication. For any emergencies at any time or if you are unable to contact a member of the research team, please attend your local accident and emergency for an assessment.

12. What happens when the research study stops?

Once the results of the MRI and, if required, biopsy are available you will be called to clinic to discuss them. Once a treatment decision is made, most men in the study will complete the study and your normal clinical team will continue to look after your care. Being part of the study does not prevent you from undergoing any further diagnostic test or treatment that your clinician would normally recommend.

13. What if there is a problem?

Any complaint about the way you have been dealt with during the clinical study or any possible harm you might suffer will be addressed. The detailed information concerning this is given in Part 2 of this information sheet. If you have any concerns or complaints you should contact a member of the research team in the first instance.

14. Will my taking part in the study be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2.

15. Will any costs I incur in travelling to study visits be reimbursed to me?

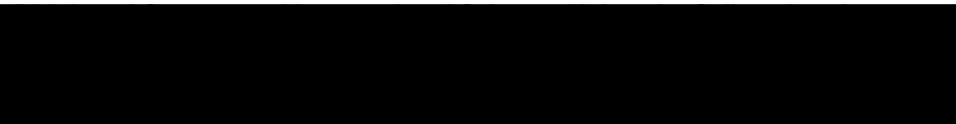
Reasonable transport costs that you incur to get to additional study visits (if any further visits are necessary) that are above what you would normally need if you were not part of the study may be reimbursed. Please contact your local study nurse or doctor or the Study Coordinator (details below) for further information on claiming.

16. Contact Details

If you have any further questions or need any further information please do not hesitate to contact the research team.

or the **Chief Investigator:**

Mr Veeru Kasivisvanathan MBBS BSc FRCS MSc PGCert PhD



This completes Part 1 of the Information Sheet.

If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making any decision.

Part 2

17. What if relevant new information becomes available?

Sometimes we get new information about the procedures being studied. If this happens and we feel it is important to your participation in the study, we will tell you about it and discuss whether you want to or should continue in the study. If you decide not to carry on, we will make arrangements for your care to continue. If you decide to continue in the study, we may ask you to sign an updated consent form. You can also find out if there is any new relevant information by visiting www.ncita.org.uk.

18. What will happen if I don't want to carry on with the study?

You can withdraw from the study at any point and it will not affect the care that you are given. We will use information collected about you up until your withdrawal. Kindly keep in contact with us to let us know your progress.

19. What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to your research team who will do their best to answer your questions, please see point number 24. You can also contact the Chief Investigators on the number or address given earlier in this document. If you wish to complain by other means or have any concerns about any aspect of the way you have been approached or treated by members of staff or about any side effects (adverse events) you may have experienced due to your participation in the clinical study, the normal National Health Service complaints mechanisms are available to you. You can contact the hospital Patient Advice and Liaison Service (PALS). Your local PALS team can be contacted at the following number:

Local team to insert contact details of local PALS office here:

You can also contact NHS helpline at 111 which will be able to give you the number of your local PALS office if you are concerned.

Every care will be taken in the course of this clinical study. However in the unlikely event that you are injured by taking part, compensation may be available.

If you suspect that the injury is the result of the Sponsor's (University College London) or the hospital's negligence, then you may be able to claim compensation. After discussing with your study doctor, please make the claim in writing to Mr Veeru Kasivisvanathan who is the Chief Investigator for the clinical study and is based at University College London. The Chief Investigator will then pass the claim to the Sponsor's Insurers, via the Sponsor's office. You may have to bear the costs of the legal action initially, and you should consult a lawyer about this.

20. Will my taking part in this study be kept confidential?

If you consent to take part in this study, the records obtained while you are in this study as well as related health records will remain strictly confidential at all times. The information will be held securely on paper and electronically at your treating hospital under the provisions of the Data Protection Act 2018 and the General Data Protection Regulations 2018. The information will be made available to persons in the clinical and research teams treating you. Your name and personal details will not be passed to anyone else outside the clinical team, research team or the Sponsor, who is not involved in the study. No additional samples will be taken specially for research in this study. All The research team may verify results of tests carried out at your local hospital (for example MRI results or prostate biopsy results) by transferring and analysing a small number of samples collected to UCL. samples and information collected will be de-identified to you prior to transfer to UCL, so only non-identifiable data will be transferred to UCL. This includes some pathology glass slides, which will be reviewed at Dr Alex Freeman's laboratory at University College London (UCL), for quality control. Slides sent to UCL will be

not have your name assigned. Samples will be sent using one of UCL's preferred couriers, for both pick up and return.

Any data stored by the research team outside of your treating hospital will be kept at a secure location and will not contain information that can directly identify you. You will be allocated a study number, which will be used as a code to identify you on all study forms and data. The information will be linked to you so that if we did need to identify you for your safety or to clarify some information we would be able to by using a unique key, which will be known only to your local hospital team.

Your records will be available to people authorised to work on the study but may also need to be made available to people authorised by the Sponsor, which is the organisation responsible for ensuring that the study is carried out correctly. By signing the consent form, you agree to this access for the current study and any further research that may be conducted in relation to it, even if you withdraw from the current study. All will have a duty of confidentiality to you as a research participant.

If you withdraw consent from further study treatment, your data and samples will remain on file and will be included in the final study analysis.

In line with the regulations, at the end of the study your data will be securely archived for 20 years. Arrangements for confidential destruction will then be made.

Anonymised data collected during the study may be transferred for the purpose of processing or analysis to approved associated researchers and commercial partners within/outside the European Economic Area. The Sponsor of the study will take all reasonable steps to protect your privacy.

In the future we may publish our findings from the study in scientific journals, but you will not be identifiable in any publications.

21. Will my GP be informed of my involvement?

Because this study is not being carried out by your GP, we would like to inform them of your participation. If you agree to take part and agree to us contacting your GP, we will give him or her details of the study and inform them that you have chosen to participate in it. You will not be able to participate in this study if you do not give us this permission to inform your GP.

22. What will happen to the results of the research study?

The results of the study will be available after it finishes and will usually be published online in a medical journal and presented at a scientific conference, they will also be posted to. The data will be anonymous and it will not be possible to identify you in any report or publication. Sometimes the data may be used to teach other healthcare professionals how to treat patients in a similar position to you.

Should you wish to see the results, or the publication, please ask your study doctor or see the trial website on <https://www.ucl.ac.uk/surgery/research/research-department-targeted-intervention/prime-trial-information>, or the clinical trials units website www.ncita.org.uk.

23. Who is organising and funding the research?

The governance sponsor is University College London. The study is funded by Prostate Cancer UK, the European Association of Urology Research Foundation, the UK National Institute for Health Research via an Academic Clinical Lectureship to Dr Veeru Kasivisvanathan and the UK National Cancer Imaging Translational Accelerator.

24. Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favorable opinion by National Research Ethics Service Committee _West Midlands - Black Country Research Ethics Committee. Patients and members of the public have also reviewed the study documents to ensure they are appropriate and well written.

25. Further information

You are encouraged to ask any questions you wish, before, during or after your investigations. If you have any questions about the study, please speak to your study nurse or doctor on the numbers specified below, who will be able to provide you with up to date information about the procedures involved. If you wish to read the research on which this study is based, please ask your study nurse or doctor.

Site Study staff contact details:

Principal Investigator (site) details:

Alternatively, if you or your relatives have any questions about this study you may wish to contact one of the following organisations that are independent of the hospital at which you are being treated:

Prostate Cancer UK – 0800 082 1616 - <http://prostatecanceruk.org>

Macmillan Cancer Support - 0808 808 0000 – <http://www.macmillan.org.uk>

If you decide you would like to take part then please read and sign the consent form. You will be given a copy of this information sheet and the consent form to keep. A copy of the consent form will be filed in your patient notes, one will be filed with the study records and one may be sent to the Research Sponsor.

You can have more time to think this over if you are at all unsure.

Thank you for taking the time to read this information sheet and to consider this study.