Comparing biparametric to multiparametric MRI in the diagnosis of clinically significant prostate cancer in biopsy-naive 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 1,12,13, Yemisi Takwoingi 12,13, Jonathan J Deeks 12,13, Caroline M Moore 1,11, Veeru Kasivisvanathan 1,11, PRIME Trial Group

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 pragmatic, prospective, international, multicentre trial being carried out in a range of different healthcare settings. PRIME will be one of the first trials to carry out qualitative assessment of diagnostic yield. 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.

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. MRI is widely established as the gold standard diagnostic imaging modality for detecting clinically significant prostate cancer (PCa). 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. 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.

Current recommendations for the use of MRI for detection of PCa focus on the use of multiparametric MRI (mpMRI). 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. 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. 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, 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 studies. The few prospective studies have not been typically robustly designed to evaluate the role of DCE in PCA detection.

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 V2.1 systems. For MRI to be suspicious it can be scored 3, 4 or 5 on either Likert or PI-RADS V2.1 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.

Objectives
The primary objective is to compare the detection of clinically significant PCAs (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 with 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 indeterminately scored MRI as reported by bpMRI and mpMRI.
- To compare the proportion of men with MRI 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
PRECISION study quality control highlighted that the image quality of the DCE sequences was the most variable sequence across sites. 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) system. 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. 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 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 V2.1 scoring systems will be used to identify any suspicious lesions in the prostate. Suspicious areas (Likert or PI-RADS V2.1 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 V2.1) 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 V2.1. 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.
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 (e.g., 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 2** Participant timeline in the trial: the timeline for men enrolled to the trial prior to undergoing MRI

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

*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 (e.g., 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; IIIE-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 ≥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% 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 significant PCa on mpMRI-targeted biopsy.

### Table 3

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

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

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.
## Table 4  WHO trial registration dataset

<table>
<thead>
<tr>
<th>Data category</th>
<th>Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary registry and trial identifying number</td>
<td>ClinicalTrials.gov: NCT04571840</td>
</tr>
<tr>
<td>Date of registration in the primary registry</td>
<td>1 October 2020</td>
</tr>
</tbody>
</table>
| Sources of monetary or material support | ► 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 | Inclusion criteria  
► Men at least 18 years of age referred with clinical suspicion of PCa.  
► Serum PSA ≤20ng/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.  
► Contraindication to prostate biopsy.  
► Unfit to undergo any procedures listed in the protocol. |

Continued
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.

Table 5  Revision chronology for amendments to protocol

<table>
<thead>
<tr>
<th>Protocol version to date</th>
<th>Reasons for amendments</th>
</tr>
</thead>
<tbody>
<tr>
<td>V.1.0, issued 24 August 2020</td>
<td>Original protocol</td>
</tr>
<tr>
<td>V.2.0, issued 27 April 2021</td>
<td>Main reasons for amendment: minor changes to make existing trial documents clearer. Main changes: ▶ 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.</td>
</tr>
</tbody>
</table>

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).

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
▶ 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.

---

Table 4  Continued
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 $\geq 2$, 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 pseudonymised 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. Authorization 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
1 Division of Surgery and Interventional Science, University College London, London, UK
2 Clinical Effectiveness Unit, Royal College of Surgeons of England, London, UK
3 Department of Urology, Whips Cross University Hospital, London, UK
4 Department of Radiology, University College London Hospitals NHS Foundation Trust, London, UK
5 Department of Histopathology, University College London Hospitals NHS Foundation Trust, London, UK
6 Centre for Medical Imaging, University College London, London, UK
7 Institute of Epidemiology and Health Care, University College London, London, UK
8 School of Population Health, The University of Auckland, Auckland, New Zealand
9 Research Department of Primary Care and Population Health, University College London, London, UK
10 National Cancer Imaging Translational Accelerator, University College London, London, UK

11 Department of Urology, University College London Hospitals NHS Foundation Trust, London, UK
12 Test Evaluation Research Group, Institute of Applied Health Research, University of Birmingham, Birmingham, UK
13 NIHR Birmingham Biomedical Research Centre, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

Twitter
Aqua Asif @AquaAsif, Arjun Nathan @ArjunSNathan, Alexander Ng @AlexBCDNg, Pramit Khetrapal @p_khetrapal, Vinson Wai @vinsonwai, Jon Piper @jontpiper, Mark Emberton @embertonMark, Jonathan J Deeks @deeksj, Caroline M Moore @cm_moore, 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 Clinical team for their support with the MARVIN database; and Sydney Lindner, Steven Leile, Jessica Sternisa, Tyler Edwards, Adam Kuip, Jon Piper from the MM 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

Contributors
Study concept and design: ANg, AA, AN, VC, PK, FG, CA, AF, SP; PL, CSC, CBG, NM, ME, RA, YT, JD, CMD. VK. Drafting of manuscript: AA, AN, CSC, CBG, RA, YT. 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 (EUA-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 (20YOY15) 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 the 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, 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.
REFERENCES