NIHR Health Technology Assessment programme

NHS National Institute for Health Research

# NETSCC, HTA

# 16 May 2012

The Health Technology Assessment programme is managed by NETSCC, HTA as part of the NIHR Evaluation, Trials and Studies Coordinating Centre at the University of Southampton.

Alpha House, University of Southampton Science Park
Southampton SO16 7NS
**Suggest a topic for research via our online form at www.hta.ac.uk/suggest**

tel: +44(0)23 8059 5586
fax: +44(0)23 8059 5639
email: hta@hta.ac.uk

**www.hta.ac.uk**

# PROMIS
# Prostate MRI Imaging Study

Evaluation of Multi-Parametric Magnetic Resonance Imaging in the Diagnosis and Characterisation of Prostate Cancer

**Developed with the NCRI Prostate Clinical Studies Group**

**Part of the NIHR National Cancer Research Network Portfolio**

ISRCTN: 16082556
MRC: PR11
UCL reference number: 11/0009
REC reference: 11/LO/0185

## Protocol Version 3.0

**02nd February 2012**

**Authorised by:**

| | | |
|---|---|---|
| **Name** | **Professor Mark Emberton** | **Signature:** |
| Role | Chief Investigator | Date: 02nd February 2012 |
| **Name** | **Dr Rhian Gabe** | **Signature:** |
| Role | Project Lead, MRC CTU | Date: 02nd February 2012 |

# GENERAL INFORMATION

**Acronym:** PROMIS

**Title:** Evaluation of Multi-Parametric Magnetic Resonance Imaging in the Diagnosis and Characterisation of Prostate Cancer

This document describes a Health Technology Assessment (HTA) funded study called PROMIS which is being sponsored by University College London (UCL). PROMIS is being conducted by UCL and the Medical Research Council Clinical Trials Unit (MRC CTU). This document is a protocol that provides information about procedures for entering patients into PROMIS. This protocol should not be used as an aide-memoire or guide for the treatment of other patients. Amendments may be necessary; these will be circulated to known collaborating investigators, but centres entering patients for the first time are advised to contact the MRC CTU, Cancer Group, London to confirm they have the most up to date version of the protocol.

If in doubt as to the procedure for registering patients or for other study queries, please contact the Trial Manager at the MRC CTU. For urgent clinical problems relating to this study, please contact the Chief Investigator, Professor Mark Emberton.

This study will comply with the principles of Good Clinical Practice (GCP) as laid down by Commission Directive 2005/28/EC and by Statutory Instrument 2004/1031 [Amendments; 2006 No. 1928]. It will be conducted in compliance with the protocol, MRC GCP, the Data Protection Act (DPA no. Z5886415) and any other appropriate requirements.

## REGISTRATIONS

**Tel: 0207 670 4777 (Mon – Fri, 09:00 – 17:00)**

## SAE NOTIFICATION

**Within one working day of becoming aware of an SAE, please fax a completed SAE form to the MRC Clinical Trials Unit on:**

**Fax: 0207 670 4818**

# TRIAL ADMINISTRATION

| | | |
|---|---|---|
| **Chief Investigator** | **Professor Mark Emberton** | T: 0207 380 9194 |
| | Division of Surgery and | F: 0207 380 9303 |
| | Interventional Sciences | E: markemberton1@btinternet.com |
| | University College London | |
| | 67 Riding House Street | |
| | London, W1P 7NN | |
| **Co-Investigators** | **Mr Hashim Uddin Ahmed** | E: hashim.ahmed@ucl.ac.uk |
| | Division of Surgery and | |
| | Interventional Science, | |
| | University College London | |
| | **Dr Christopher Parker** | E: chris.parker@rmh.nhs.uk |
| | Academic Urology Unit | |
| | Royal Marsden Hospital | |
| | **Mr Richard Hindley** | E: richard.hindley@bnhft.nhs.uk |
| | Department of Urology | |
| | North Hampshire Hospitals NHS Trust | |
| **Radiology Lead** | **Dr Alex Kirkham** | E: alex.kirkham@uclh.nhs.uk |
| | UCLH NHS Foundation Trust | |
| **Histopathology Lead** | **Dr Alex Freeman** | E: alex.freeman@uclh.nhs.uk |
| | UCLH NHS Foundation Trust | |
| **Health Economics Lead** | **Professor Mark Sculpher** | E: mark.sculpher@york.ac.uk |
| | Centre for Health Economics | |
| | University of York | |
| **Senior Scientist** | **Professor Richard Kaplan** | E: rk@ctu.mrc.ac.uk |
| | MRC Clinical Trials Unit | |
| **Project Lead** | **Dr Rhian Gabe** | E: rg@ctu.mrc.ac.uk |
| | MRC Clinical Trials Unit | |
| **Statistician** | **Khadija Rantell** | E: k.rantell@ucl.ac.uk |
| | University College London | |
| **Trial Manager** | **Cybil Kwakye** | T: 0207 670 4848 |
| | MRC Clinical Trials Unit | E: PROMIS@ctu.mrc.ac.uk |
| **Data Manager** | **Sophie Stewart** | T: 0207 670 4620 |
| | MRC Clinical Trials Unit | E: PROMIS@ctu.mrc.ac.uk |
| **Trial Co-ordination** | **Cancer Group** | E: PROMIS@ctu.mrc.ac.uk |
| | MRC Clinical Trials Unit | T: 0207 670 4700 |
| | Aviation House | Fax: 0207 670 4818 |
| | 125 Kingsway | Website: www.ctu.mrc.ac.uk |
| | London, WC2B 6NH | |

# CONTENTS

# APPENDICES

Please refer to PROMIS Protocol Appendices

# ABBREVIATIONS AND GLOSSARY

| | |
|---|---|
| **ADC** | Apparent diffusion coefficient |
| **AE** | Adverse event |
| **CI** | Confidence interval |
| **CPB** | Combined prostate biopsy |
| **CRF** | Case report form |
| **CTA** | Clinical Trials Authorisation |
| **DCE** | Dynamic Contrast Enhanced |
| **DRE** | Digital rectal examination |
| **DW** | Diffusion weighting |
| **Gd-DTPA** | Gadolinium-diethylenetriamine pentaacetic acid |
| **HE** | Health economics |
| **HES** | Hospital Episode Statistics |
| **HRQL** | Health-related quality of life |
| **HTA** | Health Technology Assessment |
| **MRC** | Medical Research Council |
| **CTU** | Clinical Trials Unit |
| **MP-MRI** | Multi-Parametric Magnetic Resonance Imaging |
| **MRI** | Magnetic Resonance Imaging |
| **NCRN** | National Cancer Research Network |
| **NHS** | National Health Service |
| **NICE** | National Institute for Health and Clinical Excellence |
| **NIHR** | National Institute for Health Research |
| **NPV** | Negative predictive value |
| **PI** | Principal Investigator |
| **PIS** | Patient information sheet |
| **PPV** | Positive predictive value |
| **PROMIS** | Prostate MRI Imaging Study |
| **PSA** | Prostate specific antigen |
| **QA** | Quality assurance |
| **QALY** | Quality adjusted life years |
| **QC** | Quality control |
| **QoL** | Quality of life |
| **ROI** | Region of interest |
| **RP** | Radical prostatectomy |
| **SAE** | Serious adverse event |
| **SOP** | Standard Operating Procedures |
| **STARD** | STAndards for the Reporting of Diagnostic accuracy studies |
| **TMG** | Trial Management Group |
| **TPM** | Template prostate mapping |
| **TRUS** | Transrectal ultrasound |
| **TSC** | Trial Steering Committee |
| **UCL** | University College London |
| **UCLH** | University College London Hospital |

# 1. SUMMARY

## 1.1 Abstract and summary

The purpose of PROMIS (MRC PR11) is to trial the use of multi-parametric Magnetic Resonance Imaging (MP-MRI) as a tool in the diagnosis of prostate cancer. In particular, PROMIS aims to evaluate whether MP-MRI improves the ability to detect as well as rule-out clinically significant prostate cancer in a group of men currently advised to have prostate biopsy.

At present, men with raised serum prostate specific antigen (PSA) are advised to have a transrectal ultrasound (TRUS) guided biopsy. This study will investigate whether imaging prior to biopsy can be incorporated into the existing diagnostic pathway for prostate cancer. We will evaluate whether men with a raised PSA, or other risk factors for harbouring prostate cancer, should first undergo a MP-MRI in order to select a group that could safely forego prostate biopsy. In addition, this study will evaluate the ability of MP-MRI to identify lesions for selective biopsy.

In order to evaluate the diagnostic accuracy of MP-MRI (index test) against the TRUS guided biopsy (current standard test) both procedures need to be compared to a reference standard. This reference standard needs to be accurate at both detecting and ruling-out prostate cancer and amenable to application to all men at risk. Template Prostate Mapping (TPM) meets the necessary performance characteristics of such a reference test. It is performed under a general/spinal anaesthetic.

By design, PROMIS, conforms to a validating paired cohort study (see Oxford Centre for Evidence-based Medicine, 'Levels of Evidence', 1b, http://www.cebm.net/index.aspx?o=1025). All men in the study will have a MP-MRI (index test), followed by both a TPM biopsy (reference test) and a standard TRUS guided biopsy (current standard test). These 3 tests will be assessed and reported independently from each other.

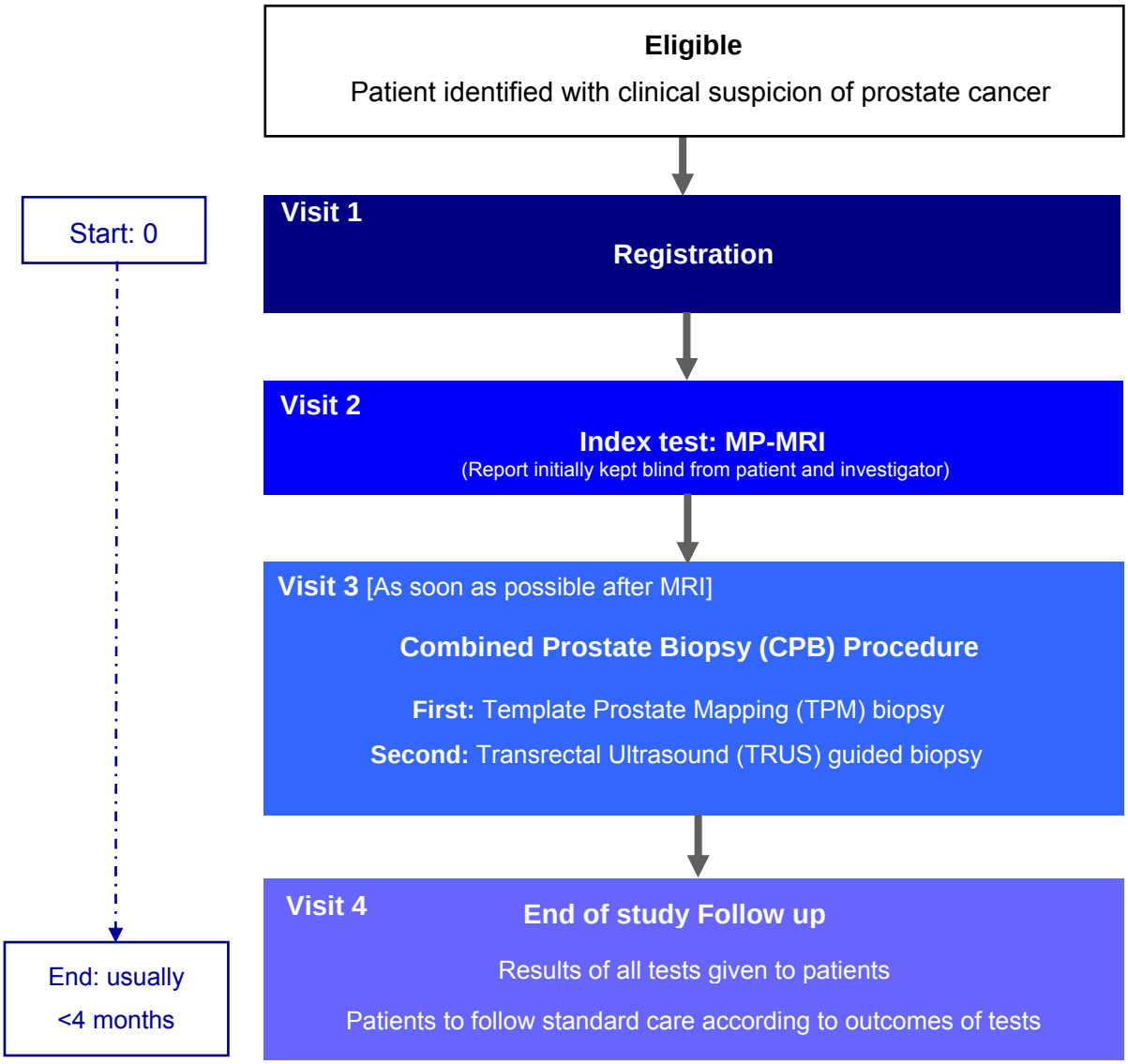
The study is divided into a pilot and a main phase. The pilot will be run in two centres, University College London Hospitals NHS Foundation Trust and North Hampshire Hospitals NHS Trust and aims to recruit 50 patients over one year. The pilot will assess recruitment and the safety of administering the tests, particularly the combined prostate biopsy (CPB) procedure of TPM and TRUS under general/spinal anaesthesia. Continuation to the main phase will depend on an independent review of the data.

The main phase will be extended to approximately 6 centres in total (including the 2 pilot centres), recruiting up to 714 men to have all 3 tests over an additional 2 to 3 years.

The main objectives of the trial are:

- To assess the ability of MP-MRI to identify men who can safely avoid unnecessary biopsy.
- To assess the ability of the MP-MRI based pathway to improve the rate of detection of clinically significant cancer as compared to TRUS biopsy.
- To estimate the cost-effectiveness of an MP-MRI based diagnostic pathway. Using data from the main study and the wider literature, the study will consider the implications of alternative diagnostic strategies for NHS cost and men's quality-adjusted survival duration.

## 1.2 Trial schema




**Primary Outcomes**

**Pilot Phase**

1. Safety
2. Recruitment

**Main Trial**

1. Proportion of men who could safely avoid biopsy as determined by specificity and negative predictive values
2. Proportion of men correctly identified by MP-MRI to have clinically significant prostate cancer as determined by sensitivity and positive predictive values

# 2. INTRODUCTION & BACKGROUND

## 2.1 General overview and rationale

There are approximately 35,000 new cases of prostate cancer annually in the UK. The incidence has doubled in the last 15 years, mainly due to increased use of serum Prostate Specific Antigen (PSA) testing in healthy men. As a result, prostate cancer has become the most common cancer in men.[1] The existing diagnostic pathway will, if left unchecked, result in a further rise in incidence and associated costs to the NHS without necessarily reducing the risk of dying from the disease. Many, if not most, prostate cancers that are currently detected are clinically insignificant. Therefore, over-diagnosis, the detection of a cancer that would not have had any clinical impact on the individual during his remaining life, is a major problem.

This assertion has received considerable support from two large randomised controlled trials of prostate cancer screening. While the US screening trial showed no evidence of a survival benefit,[2] the European Screening study showed a modest reduction in risk of death from prostate cancer in those screened.[3] The number needed to screen was 1410 and the number needed to treat 48 to extend the life of one man over a ten year period.[4] Commentators were quick to voice their concern that over-diagnosis, and hence over-treatment and associated morbidity, would increase further if PSA screening were adopted more widely.[5 6] However, if a diagnostic method was available that was more specific for *clinically significant* prostate cancer, the beneficial effect of screening on mortality could be retained, while minimising over-diagnosis and over-treatment.

## 2.2 Diagnostic pathway

At present, a man is judged to be at risk of harbouring prostate cancer if he has any of the following: a raised serum PSA level (the majority), an abnormal digital rectal examination (DRE), a positive family history or a specific ethnic risk profile. Such men are currently advised to have a transrectal ultrasound (TRUS) guided prostate biopsy. Between 59,000 and 80,000 men have a TRUS biopsy in the UK each year. Men undergo prostate biopsy in the absence of accurate imaging that can visualise a suspicious lesion. Ultrasound is used to identify the prostate, not the suspect lesion. The result is that biopsies are taken 'blindly' from areas of the gland. This approach (Figure 1, current diagnostic pathway) contrasts markedly with that used for other cancers. The typical approach is either to see (e.g. at endoscopy) or to image (e.g. using mammography) a suspect lesion, and then to biopsy it directly.

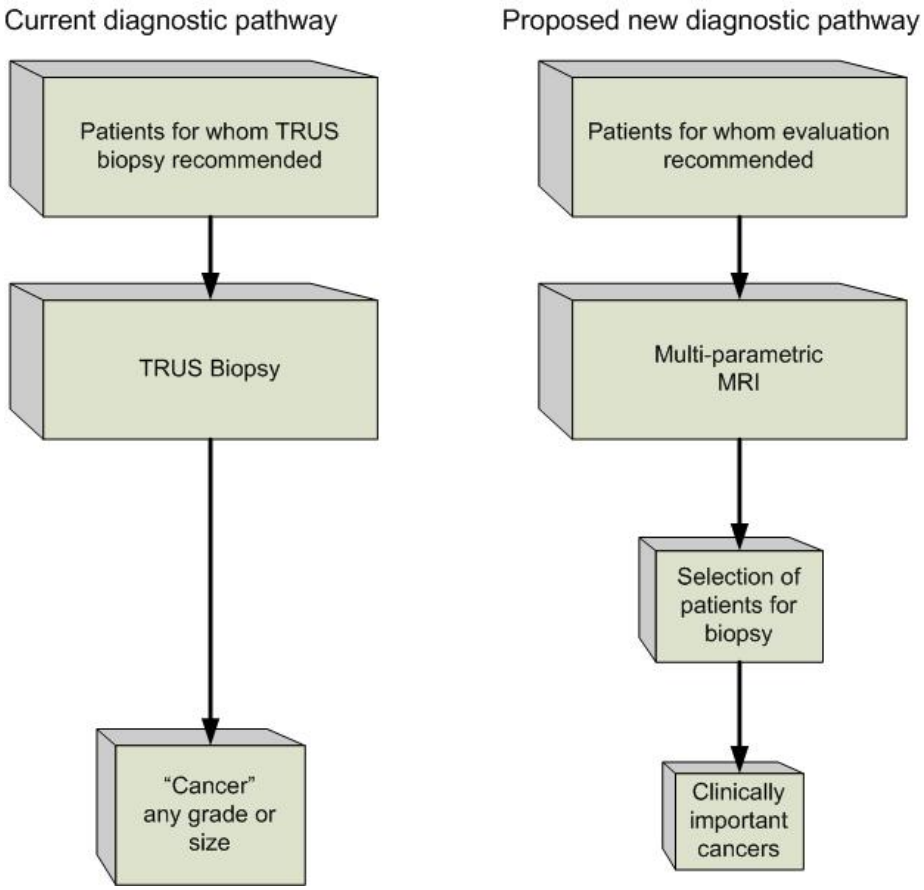
In PROMIS, we will determine whether it is appropriate that men with a risk factor for harbouring clinically significant cancer should first undergo MP-MRI to select who should, or should not, have a prostate biopsy. MP-MRI would therefore act as a triage test (Figure 1, proposed diagnostic pathway).[7] This could offer several important advantages:

- **Less over-diagnosis,** i.e. fewer *clinically insignificant* prostate cancers detected by avoiding unnecessary biopsy of men who do not have clinically significant cancer.
- **Less over-treatment** as fewer *clinically insignificant* prostate cancers are detected.
- **Increased detection of *clinically significant* prostate cancers** by directing biopsies to areas of the prostate that appear abnormal on MP-MRI.
- **Improved characterisation of individual cancers** due to more representative biopsy sampling.

- **Reduced complications (sepsis and bleeding)** as fewer men biopsied and fewer biopsies taken in men that are biopsied.

The overall result also has the potential to offer a more cost-effective use of NHS resources. This area of research has been designated as important both by the UK's National Institute for Health and Clinical Excellence (Prostate Cancer Management Guidelines, 2009)[8] and the US National Institute of Health - National Cancer Institute.[9]

**Figure 1: Current and proposed diagnostic pathway for prostate cancer**



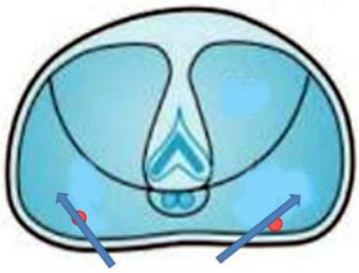

Please note: this is a proposed future diagnostic pathway and NOT the pathway patients will take in PROMIS (See Trial Schema 1.2)

## 2.3 Prostate biopsy

### 2.3.1 Over-detection of insignificant prostate cancer

Middle-aged men in the general population who undergo TRUS biopsy have a 25% chance of being diagnosed with prostate cancer.[10] This compares with a lifetime risk of 6-8% for symptomatic prostate cancer, and illustrates the over-diagnosis of harmless cancers in many men who undergo TRUS biopsies (Figure 2).[11]

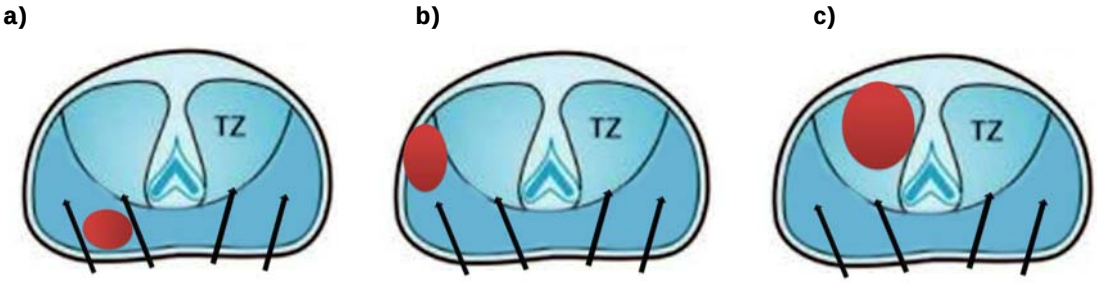
**Figure 2: Over-detection of insignificant prostate cancer**



### 2.3.2 Under-detection of clinically significant prostate cancer

TRUS biopsies have an estimated false negative rate of 30%-45%.[12 13] The clinician takes 10-12 biopsies in a manner that attempts to obtain representative tissue within the peripheral zone (Figure 3a). However, several parts of the gland are not well sampled using this approach (systematic error). The anterior part of the gland may be missed as a result of its greater distance from the rectum (Figure 3b, 3c). Tissue in the midline is missed due to efforts to avoid the urethra, while the apex of the prostate is often inaccessible by the transrectal route.

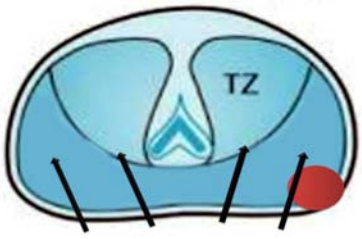
**Figure 3: Under-detection of clinically significant prostate cancer**




### 2.3.3 Inaccurate risk stratification

TRUS biopsies can be unrepresentative of the true burden of cancer due to random sampling error (Figure 4). Either the size or the grade of cancer may be underestimated if the cancer tissue obtained on TRUS biopsy is not representative.[14] Figure 4 illustrates how accurate estimation of tumour size will depend on hitting the centre of a lesion. At present, because these lesions are not visualised, this relies purely on chance. However, improved risk stratification is likely if MRI results can be used to guide TRUS biopsies.

**Figure 4: Inaccurate risk stratification**



The pathological status derived from TRUS biopsies can be unreliable if the test is reapplied, not only at discriminating clinically important cancer from clinically unimportant prostate cancer but also at attributing a non cancer status from a cancer status in about a quarter of men subject to serial testing.

### 2.3.4 Side effects

TRUS biopsy is associated with a number of complications, the most important being urinary tract infection (1-8%) that can result in life-threatening sepsis (1-4%). Haematuria (50%), haematospermia (30%), pain/discomfort (most), dysuria (most) and urinary retention (1%) can also be expected.

## 2.4 MRI

### 2.4.1 Diagnostic accuracy of MRI in prostate cancer

The evidence base suggests that MRI can achieve both a sensitivity and specificity between 70-90% for the detection of clinically significant prostate cancer.[15] However, a systematic review of the literature,[16] found the quality of the initial studies evaluating MRI to be disappointing (see section 2.4.3).[17] They repeatedly showed low sensitivity and specificity as well as high inter-observer variability, even when using high resolution endorectal MRI.[18-24] Since these early reports, much has changed including an appreciation of the impact of post-biopsy changes on MRI, technological improvements such as increasing magnetic field strength (from 0.5 Tesla to 1.5 Tesla and 3.0 Tesla), shorter pulse sequences enabling faster image acquisition, and the introduction of functional imaging in the form of diffusion weighting (DW) and dynamic contrast-enhancement (DCE).

The main types of MR images available are those produced by T2 weighting (T2), diffusion weighting (DW) and dynamic contrast enhancement (DCE). Each MR parameter in isolation has been reported to have the range of sensitivity and specificity shown in Table 1. For more information of the main types of MR images please see Appendix I: Main types of MR images.

### 2.4.2 MP-MRI

Multi-parametric approaches (combining these 3 sequences together) have also been investigated. Although small, single centre case series have found an advantage for using two or three MR sequences rather than just one. None have evaluated the clinical validity of MP-MRI in the population of interest against an accurate and appropriate reference standard within a multi-centre study.[25-35]

**Table 1: Sensitivity and specificity of MRI parameters as reported in the literature**

| Parameter | Number (mean) | Sensitivity | Specificity |
|---|---|---|---|
| T2 | 12-320 (97) | 37-96% | 21-67% |
| DW | 11-95 (42) | 57-90% | 79-88% |
| DCE | 23-54 (41) | 71-87% | 61-89% |

### 2.4.3 MRI literature limitations

There are important limitations with previous studies investigating the diagnostic accuracy of MRI for prostate cancer:

- **Biopsy artefact:** studies mostly evaluate MRI after biopsy. However the biopsy procedure can affect what is seen on the MRI which can result in an increase in false positive or negative results.
- **Limited application:** studies mostly evaluate only the peripheral zone of the prostate, ignoring up to one third of prostate cancers.
- **Segmentation:** when each region of interest (ROI) is segmented to achieve sufficient datasets, increasing the power of the analysis and accuracy by incorrectly treating each ROI as independent.
- **Poor reference standard:** most studies use radical prostatectomy (RP), leading to selection bias as those undergoing surgery tend to have burdens of cancer that are distinct from men with an abnormal PSA, and patients choosing other treatments can never be evaluated.[36] Co-registration of an image to an RP specimen is challenging because of shrinkage (10-20%), distortion, tissue loss as a result of 'trimming' (10%), orientation, and absent perfusion.

These deficiencies probably account for the limited acceptance of MRI in contemporary prostate cancer diagnostic pathways.[37]

## 2.5 Template Prostate Mapping (TPM)

TPM has been selected as the reference test for this study as it meets the required specification for our defined population when using 5mm-sampling[38] (Appendix II: Template Prostate Mapping Protocol, Figure A1):

- TPM produces a histological map of the entire prostate in 3-dimensions.[39-42]
- TPM has estimated sensitivity and negative predictive value (NPV) in the order of 95% for clinically significant cancers when assessed against radical prostatectomy.[43-45]
- TPM avoids selection bias since all men exposed to the index test can be exposed to the reference standard.
- TPM has a similar side effect profile to that of TRUS biopsy with 3 important differences:
    - TPM carries a significantly lower risk of urosepsis (<0.5%) – the most serious complication of TRUS biopsy - as the needles do not traverse rectal mucosa
    - TPM confers a higher risk of self-limiting failure to void urine (5%) as a result of greater gland swelling[41 46 47] compared to 1-2% associated with TRUS biopsy
    - TPM requires a general/spinal anaesthetic

Although the accuracy of TPM is high in the diagnosis of prostate cancer, it is not currently recommended for standard practice since more research is required on its implementation.[48] For more information on TPM Protocol please see Appendix II.

To compare the diagnostic accuracy of MP-MRI (index test) against the TRUS guided biopsy (current standard) both need to be individually compared to TPM (reference standard). Therefore, all patients in the proposed study will undergo all 3 tests (MP-MRI, TPM and TRUS) but the results will be assessed independently by different people. However, it should be noted that the TPM followed by the TRUS will be performed as a combined prostate biopsy (CPB) procedure.

## 2.6 Definition of clinically significant prostate cancer

MP-MRI (index test) will be assessed against two definitions of clinically significant prostate cancer derived from TPM (reference test). DEFINITION ONE (to be used in measurement of the primary outcomes) and DEFINITION TWO of clinically significant prostate cancer are given in the box below:

| | | |
|---|---|---|
| **DEFINITION ONE (PRIMARY):** | Dominant Gleason pattern ≥ 4<br>Cancer Core Length ≥ 6 mm | AND/OR |
| **DEFINITION TWO:** | Any Gleason pattern ≥ 4<br>Cancer Core Length ≥ 4 mm | AND/OR |

## 2.7 Trial design

The study is a prospective validating paired cohort study. All men in the study will have a MP-MRI, followed by the CPB procedure (TPM followed by TRUS) and each test will be assessed and reported independently from each other (See Trial Schema 1.2). The study will be run in two stages: the pilot phase, followed by the main phase.

The pilot study aims to recruit 50 patients. These will be recruited from two centres (University College London Hospitals (UCLH) NHS Foundation Trust and Basingstoke and North Hampshire NHS Foundation Trust) over one year. It will allow us to:

- Prospectively record the rate of sepsis following the CPB procedure*.
- Monitor recruitment rate.
- Provide an estimate of the prevalence in the scanned population of prostate cancer according to DEFINITION ONE and DEFINITION TWO.
- Provide estimate of key outcome measures (sensitivity and specificity of MP-MRI compared to TPM, inter/intra-observer reliability of the MP-MRI).
- Provide evidence which, together with data from the literature, will facilitate a preliminary assessment of cost-effectiveness which, in turn, will feed into an assessment of the key design features of the main study.

* While it is anticipated that the sepsis rate will be low,[49] each event will be reviewed by the TMG and, as appropriate, by the independent Trial Steering Committee (TSC). If deemed necessary for safety reasons, recruitment to the study will be suspended.

Continuation to the main phase will be dependent on the review of the pilot phase by the TSC. The main phase will involve at least six centres recruiting up to 714 men to have the MP-MRI and CPB over an anticipated additional 2 to 3 years. There will be ongoing central safety monitoring and regular review for safety and data quality.

## 2.8 Translational research

Subject to securing future funding to collect additional blood and urine samples, the following translational objectives will also be addressed in this protocol:

- Clinical validity (sensitivity, specificity, negative and positive predictive values, overall accuracy) of the following biomarkers in the detection of clinically significant prostate cancer:
  - Free/Total PSA
  - Urinary PCA3
  - TMPRSS-ERG gene fusion
  - Ultrasound tissue characterisation
- A tissue bank will be established comprising pre and post-DRE urine, serum, plasma and germline DNA for evaluation of future candidate diagnostic markers with respect to TPM findings (tissues collected prior to CPB procedure).

# 3. SELECTION OF CENTRES/CLINICIANS

The study will consist of designated centres (subject to approvals), that have undergone formal training and quality control in conducting and reporting pre-biopsy MP-MRI and the CPB procedure. Centres will be approved by the TMG prior to participation and attendance at training is a pre-requisite for a centre being approved (see section 6.6).

All designated centres should be registered with the MRC CTU. The MRC CTU and the sponsor must receive the following documentation before a centre can be approved to register patients to PROMIS:

- Copy of approval from the centre's Trust R&D department.
- Signed model agreement for non-commercial research in the NHS.
- Full contact details for all site personnel.
- Completed signature list and delegation of responsibilities log. The MRC CTU must be notified immediately of any changes to trial personnel and/or their responsibilities. An up to date copy of this log must be stored in the Trial Master File at the site and also at the MRC CTU. The delegation log will record who is trained to carry out the MP-MRI and biopsy procedures.
- Copies of the most recent version of the patient information sheet (PIS), GP letter and consent form on local headed paper.
- Completed normal ranges form for site.
- Procedure training log, with at least one named responsible person to conduct MP-MRI and CPB.

Once all of this documentation has been received, confirmation of approval to begin recruitment will be sent to the Principal Investigator (PI) at each institution by the trial team at the MRC CTU.

Before a patient is registered, written informed consent must be obtained. The approved PIS and informed consent form are supplied by the MRC CTU and should be presented on local headed paper.

# 4. SELECTION OF PATIENTS

Patients will be considered eligible for registration into this study if they fulfil all of the inclusion criteria and none of the exclusion criteria, as defined below.

## 4.1 Patient inclusion criteria

1. Men at least 18 years or over at risk of prostate cancer who have been advised to have a prostate biopsy
2. Serum PSA ≤ 15ng/ml within previous 3 months
3. Suspected stage ≤ T2 on rectal examination (organ confined)
4. Fit for general/spinal anaesthesia
5. Fit to undergo all protocol procedures including a transrectal ultrasound
6. Signed informed consent

## 4.2 Patient exclusion criteria

1. Treated using 5-alpha-reductase inhibitors at time of registration or during the prior 6 months
2. Previous history of prostate biopsy, prostate surgery or treatment for prostate cancer (interventions for benign prostatic hyperplasia/bladder outflow obstruction is acceptable)
3. Evidence of a urinary tract infection or history of acute prostatitis within the last 3 months
4. Contraindication to MRI (e.g. claustrophobia, pacemaker, estimated GFR ≤50)
5. Any other medical condition precluding procedures described in the protocol
6. Previous history of hip replacement surgery, metallic hip replacement or extensive pelvic orthopaedic metal work.

**Please contact the PROMIS Trial Manager before registering a patient if you have any queries concerning patient eligibility.**

# 5. REGISTRATION PROCEDURE (VISIT 1)

## 5.1 Screening procedures

The PI must keep a screening and enrolment log of all patients being considered for PROMIS. These logs will be provided by the MRC CTU at centre accreditation.

## 5.2 Obtaining written informed consent

Men at risk of prostate cancer who have been advised to have a prostate biopsy will be invited to join the study. Potential participants will be approached by a study clinician or research nurse (who is a member of their direct clinical care team). Patients interested in participating in the study, will be given a PIS to read and at least 24 hours, as per national standards, to consider the study. Patients will be given email, telephone and postal contact details if they wish to address any queries or concerns. It will be emphasised that were patients to refuse participation, their continued care will not be affected in any way. **Consent must be obtained by an authorised clinician before any trial-specific patient assessments are carried out.**

### 5.2.1 Pre-registration investigations

- **PSA:** it is a requirement of the eligibility criteria that a PSA test has been carried out within 3 months of registration. Results are required for registration. If this test has been done as part of standard care and within the 3 month timeframe, there is no need to repeat this test. However, if the PSA test has not been completed, it should be carried out after consent has been obtained and prior to registration.
- **Free/Total PSA:** If this test has been done as part of standard care within 3 months of registration and the results are available, then there is no need to repeat this test. However, if the Free/Total PSA test has not been completed and it is possible to collect, it should be carried out after consent has been obtained and prior to registration.
- **Blood and urine sample collection:** Only to be taken if the patient has agreed to this option on the consent form. The blood samples should be taken after consent and before the combined biopsy procedure. Urine samples should be taken before and after DRE (see below).
- **Digital rectal examination (DRE):** it is a requirement of the eligibility criteria that a patient must have suspected stage ≤ T2 on rectal examination (organ confined). Results are required for registration. DRE should be carried out after consent has been obtained and prior to registration if:
    - a consenting patient is having urine samples collected, or
    - DRE has not been already been completed within the 6 months prior to registration.

  However, if the patient is not having urine samples collected and DRE has been done as part of standard care within the 6 month timeframe there is no need to repeat this test.
- **EQ-5D (Appendix III):** this should be completed after consent has been taken.

## 5.3 Visit 1: Registration

Please confirm patient eligibility and complete the registration form before telephoning the MRC CTU. During this telephone call, the patient will be allocated a unique identification number which will be used in all correspondence. Confirmation of the details provided at registration will be sent within one working day of entry.

**REGISTRATIONS**

**Tel: 0207 670 4777 (Mon – Fri, 09:00 – 17:00)**

# 6. PROCEDURES, ASSESSMENT & FOLLOW-UP (VISITS 2-4)

All patients will have a MP-MRI of the prostate as the index test. At a separate visit, patients will undergo two biopsies combined within the same procedure (see Trial Schema 1.2): the template prostate mapping (TPM) and a TRUS guided biopsy of the prostate.

The MP-MRI should be done as soon as possible following patient registration. The two biopsies will be done under the same general/spinal anaesthetic and should be carried out within a maximum of 3 months after the MP-MRI. TPM will be performed prior to the TRUS guided biopsy (within the same procedure).

A follow-up visit will occur after the biopsies where results of all tests will be given to patients (usually within 4 weeks of the combined prostate biopsy (CPB) procedure. This will be the end of patient follow-up in this study.

## 6.1 Visit 2: MP-MRI

The MP-MRI will be carried out in a 1.5 or 3.0 Tesla scanner with the patient in the supine position. T2, DW and DCE scans will be acquired.

The primary analysis will be based on the local site radiology report. Clinical details including PSA and DRE findings will be known to the reporter. In addition, to determine inter-observer variability and as a quality control measure, double-reporting will be carried out centrally by a number of designated radiologists who will also know clinical details of the case.

Scans will be reported to the MRC CTU on the MRI case report form (CRF) and kept locally by the local site radiologist. Radiologist should refer to the MRI Standard Operating Procedure (SOP). Scans deemed unreadable should be repeated in the same patient whenever possible and appropriate to do so. Cases where MRI scans could not be done/are not readable and are not repeatable should be noted on the MRI CRF that is sent to the MRC CTU (Please see Withdrawal section 6.10 for further information).

An overall whole prostate score will be given (1-5) to indicate the probability of clinically significant cancer:

- Highly likely benign (1).
- Likely benign (2).
- Equivocal (3).
- Likely malignant (4).
- Highly likely malignant (5).

**For the primary outcome, an overall score of 3 or more will be used to indicate the possible presence of clinically significant cancer.** This reflects the level at which further tests (e.g. biopsy) would be considered if MP-MRI were to be introduced into the diagnostic pathway in the future.

Each reporter will have access to a workstation with mean curve software to be used in the scoring of suspicious lesions (up to a maximum of 6). Images will be reported in sequence: T2 → T2+DW → T2+DW+DCE and a separate report produced for each combination of sequences.

For sector analysis, the prostate will be divided into 12 regions of interest (ROI):

- Apex: Right/Left & Anterior/Posterior.
- Mid: Right/Left & Anterior/Posterior.
- Base: Right/Left & Anterior/Posterior.

Radiologists will use the 1-5 score for each ROI.

For each lesion found, the following will be recorded:

- Longest axial diameter.
- Lesion volume.
- Apparent Diffusion Coefficient (ADC).
- DCE-MRI curve shape.

To assist the sector analysis, radiologists will draw the locations of lesions on the 27 ROI diagram (See Appendix IV) which incorporates the 1.7cm line from the back of the prostate gland. This will involve declaring the suspected positives only. The radiologist will also report the likely co-ordinates at which they would expect cancer to be positive on TPM.

MP-MRI scans will be reported on the MRI CRF and filed with the MRC CTU and with the local radiologist before the biopsy procedures are carried out. **These results must be kept blinded. Results must not be reported to the clinician performing TPM/TRUS biopsies**. Reports will only be released to the study doctor by the MRC CTU after the CPB procedure has been performed (see section 6.8). Please refer to the PROMIS MRI SOP for more detail on this procedure.

## 6.2 Visit 3: Combined Prostate Biopsy (TPM + TRUS)

TPM will be performed first under the same general/spinal anaesthetic as the TRUS guided biopsy. The biopsy procedure is combined to reduce patient burden (two visits, two procedures) and also to minimise drop out of patients between biopsies. Biopsies will be taken every 5mm throughout the prostate using a template grid placed over the perineum. Biopsies will be oriented and individually identified to facilitate later correlation of results with imaging.

TRUS guided biopsy of the prostate is to be performed after TPM, under the same general/spinal anaesthetic. This helps ensure results are obtained for the reference test in a biopsy naïve gland that has not undergone swelling and distortion to allow better post-study comparisons of the TPM and MRI findings. It also minimises the risk of infection.

The surgeon performing the CPB procedure will be blind to the MRI results. TRUS guided biopsies will be done in the left lateral position. 10-12 core biopsies will be taken as per national guidelines. Each core will be identified and potted separately. The TPM and TRUS biopsy sets from a particular patient will be sent to different pathologists to minimise bias. The pathologists will independently report results to the MRC CTU on the separate TPM and TRUS electronic CRFs. Please refer to the PROMIS Combined Biopsy SOP.

## 6.3 Visit 4: End of study visit

The last study visit should take place within approximately one month of the CPB procedure. At this visit the clinician will discuss the results of all 3 study tests (MP-MRI, TPM biopsy and TRUS biopsy) with the patient. Any side-effects of the tests experienced by the patient can be discussed. This visit marks the end of the study for the patient. Patients will be managed according to standard care in view of the results of the study tests.

## 6.4 Additional diagnostic tests

Subject to securing future funding, additional diagnostic tests will be included for evaluation of the translational objectives in this study:

- Pre and Post DRE urine (including PCA3, TMPRSS-ERG gene fusion, MSMB): on day of consent (Visit 1).
- Blood for serum and germ-line DNA: for biobanking and analysis of named biomarkers (kallikrein panel, PTEN glycoprotein panel) on day of consent or MP-MRI (Visit 1 or Visit 2).
- 3-D ultrasound volume file and radio-frequency back scatter files including Histoscanning™: immediately prior to TPM and TRUS guided biopsies at time of general/spinal anaesthetic (Visit 3).

Patients can opt out of these additional diagnostic tests if they wish, without compromising the overall primary objectives of the study as they can continue to have the MP-MRI, TPM and TRUS biopsy.

## 6.5 Long-term follow up

The group of men who consent to participate in this study will represent a uniquely characterised group. The long term outcomes of the PROMIS cohort of men will be of interest and contribute to our understanding of the epidemiology of prostate cancer. Whilst the trial is one that aims to validate MP-MRI as a diagnostic test, men who specifically consent to longer term data collection will be flagged and followed-up using the Office for National Statistics and NHS databases (see PROMIS Registration Consent Form). For example, linkage to Hospital Episode Statistics (HES) may give valuable information on further diagnoses, treatments and outcomes beyond the timeframe of the study for future analyses.

Consenting men may additionally be contacted in future to assess their willingness to respond to questionnaires. This allows the potential for research that would complement the planned long-term follow up in terms of health status, for example picking up future biopsies not included in HES, and allow assessment of quality of life.

## 6.6 Procedure training, quality control and quality assurance

### 6.6.1 MP-MRI

All radiologists from non-UCLH centres working on PROMIS will attend UCLH for a minimum of one training day on the conduct and reporting of MP-MRI. Only radiologists attending the training day (or other approved training programme if they cannot attend the training day) will be approved for reporting MP-MRIs within this trial.

Quality control (QC) and quality assurance (QA) of the MP-MRI will be outsourced to an independent commercial partner after a process of tender.

### 6.6.2 CPB procedure

Training will be provided to all centres to conduct TPM. All clinicians carrying out template biopsies will be required to carry out the procedure to the standard laid down in this protocol:

- Any number of credentialed clinicians at each centre may carry out this procedure.
- Each clinician carrying out the combined procedure will need to observe a minimum of three template biopsies at a training centre (Basingstoke or UCLH).
- Each clinician will then need to be proctored for the first 6 cases by an approved expert proctor. This may be extended at the discretion of the proctor.

Clinicians will be signed off for non-proctored cases by an expert proctor. Only clinicians approved through this programme can conduct the CPB procedure for the purpose of this study.

## 6.7 Data collection and returns

Table 2 shows the case reports forms (CRF) that are to be collected at each visit. An additional SAE form will be provided for completion as required during the study (see section 7). Please refer to PROMIS CRF completion guidelines for further details.

**Table 2: Data collection timelines**

| CRF | Screening, Consent & Registration Visit 1 | MP-MRI Visit 2 | CPB Visit 3 | Follow-up results Visit 4 |
|---|---|---|---|---|
| Registration | X | | | |
| EQ-5D Questionnaire | X | X | X | X |
| MP-MRI Reporting Form | | X | | |
| CPB Procedure Checklist | | | X | |
| TPM Reporting Form | | | X | |
| TRUS Reporting Form | | | X | |
| End of Study | | | | X |
| SAE | Complete as required at any time following patient registration | | | |
| Withdrawal Form | Complete as required at any time following patient registration | | | |

## 6.8 Blinding

### 6.8.1 Blinding of MP-MRI results

In order to make sure that the result of the MP-MRI does not influence the conduct of the biopsy, the results of the MP-MRI will not be revealed to either the men having the biopsies nor to the clinicians undertaking the biopsies until after the results of the TRUS guided biopsy and TPM are available (with one exception for unblinding given below). This blinding is necessary to prevent the results of the MP-MRI leading to some change in how the biopsies are conducted and to protect against the possibility that MP-MRI may be made to look either better or worse than it truly is in detecting and/or ruling-out significant cancer. It is essential that

the key reference test (TPM) is done in a truly systematic way so that the MP-MRI prediction can be compared to the appropriate tissue sample. Whilst accepting that TRUS biopsies under general/spinal anaesthetic may be carried out better than standard care (under local anaesthetic), it is also important that the conduct of TRUS guided biopsies is also blind to the MP-MRI so no targeting of suspicious areas occurs.

Radiology reports will be submitted directly and securely to MRC CTU. The CPB procedure will be conducted by someone other than the MRI reporter. Please refer to the PROMIS MRI SOP for more detail.

### 6.8.2 Blinding of biopsy results

To minimise bias between assessment of the TPM and TRUS biopsies, cores from TPM and TRUS biopsy procedures will be sent to different pathologists who will independently report results to the MRC CTU. Please refer to the PROMIS Combined Biopsy SOP for more detail.

### 6.8.3 Unblinding

For safety purposes, the results will be unblinded if the MP-MRI reveals apparent T4 prostate cancer or involved lymph nodes or colorectal/bladder invasion. This information will be provided to the treating clinician for appropriate clinical decision making. For some of these patients, the template mapping biopsies may be considered by the clinician as not providing useful additional clinical information and would, therefore, not be warranted, although TRUS guided biopsies are usually performed. Patients in this situation will exit the study and standard care followed. Further patients will be recruited (see section 9.2.4) to maintain the number of patients undergoing the study procedures (MP-MRI & CPB procedure).

## 6.9 Loss to follow-up

As the period of follow-up is relatively short, at approximately 4 months, there should be minimal problems with loss to follow-up in this study. Incomplete or late CRFs will be requested from the centre by the PROMIS Trial Manager at the MRC CTU. Circumstances and reasons why a patient is lost to follow-up should be detailed in writing to the Trial Manager and a copy filed in the patient's records.

## 6.10 Withdrawal

In consenting to the study, patients are consenting to study monitoring, imaging and biopsy procedures, follow-up, data collection and analysis. Patients are allowed to withdraw consent at any stage, however this is expected to be a very rare occurrence. Withdrawal may be complete (i.e. from further study procedures and any follow up), or partial (e.g. from study procedures but allowing the possibility of further follow up). All communication surrounding the withdrawal should be noted in the patient's records, and where withdrawal is complete no further PROMIS CRFs should be completed for that patient. Data up to the time of withdrawal can be included in the study if anonymised.

The MRC CTU should be informed of any patient withdrawals by sending in a completed Withdrawal Form. Patients registered into PROMIS but for whom there is no subsequent MP-MRI result or will not go on to have one or more of the study procedures should be withdrawn from the study and any remaining procedures.

## 6.11 Study closure

The study will be considered closed 30 days after the last patient has had their final follow-up visit (Visit 4).

# 7. SAFETY REPORTING

## 7.1 Safety monitoring during the pilot study

During the pilot study, the rate of sepsis following the CPB procedure will be prospectively recorded. Between 1% and 4% of patients undergoing TRUS guided biopsy alone develop sepsis requiring hospital admission, while the sepsis rate for TPM alone is <0.5%. This is because unlike the TRUS biopsy, TPM it is not administered via the transrectal route.

Although anticipated to be rare, each sepsis case will be reviewed by the TMG and where necessary by the Trial Steering Committee (TSC). Two sepsis cases out of the 50 patients in the pilot study would represent a sepsis rate of 4%. The TSC will review safety (sepsis, urinary retention) at completion of the internal pilot study, or sooner if 2 sepsis cases requiring hospitalisation are seen (and subsequently after a 2 further cases if necessary).

If the combination of TRUS and TPM leads to more than 2 cases of sepsis at any time (requiring hospital admission), there could be cause for concern and a requirement for modification of the study design. If deemed necessary for safety reasons, recruitment to the study will be suspended either during the pilot or the main phase of the study when ongoing safety monitoring would continue.

The TSC will make a recommendation regarding proceeding to the main phase which could include a modification to the study design. For example, if a sepsis rate of 10% (n=5) is observed the study remains viable but one of the following two options could be considered: (i) introducing an interval of 6 weeks between the TRUS biopsy and the TPM (which will likely lead to increased drop-out of patients) or (ii) dropping the TRUS biopsy from the study (which will prevent an analysis of the performance of TRUS biopsy but will not compromise the primary objective of the study). The TMG would seek independent recommendation from the TSC regarding these decisions.

## 7.2 SAE reporting

University College London is the trial sponsor and has delegated responsibility for the reporting of SAEs to the MRC CTU. In PROMIS, SAEs in the first instance should therefore be notified to the MRC CTU within one working day of becoming aware of the event, and the MRC CTU will notify UCL of all SAEs and the research ethics committees as appropriate.

Since there is no medicinal intervention in this study, there are no formal toxicity assessments. We expect adverse events to be rare in the context of this study, with the interventions being MP-MRI scanning and the CPB procedure. Potential safety issues are given in Table 3.

**Table 3: Potential safety issues**

| Procedures / Side effect | MP-MRI | TRUS guided biopsy | TPM biopsy |
|---|---|---|---|
| Pain/discomfort | Intravenous cannula insertion is common and causes minimal discomfort | Almost all | Pain is rare<br><br>Almost all have perineal discomfort |
| Dysuria | Not applicable | Almost all | Almost all (self-resolving within 24 hours) |
| Haematuria | Not applicable | 50% (self-resolving, 2-3 days) | Almost all (self-resolving, 1-3 days) |
| Haematospermia | Not applicable | 30% (2-3 months to resolve) | Almost all (3-6 months to resolve) |
| Erectile dysfunction | Not applicable | About 30% (self-resolving after 6-8 weeks) | Almost all (self-resolving after 6-8 weeks) |
| Urinary tract infections | Not applicable | 1-8% | <0.5% |
| Systemic urosepsis | Not applicable | 1-4% | <0.5% (lower risk than TRUS - as needles do not traverse rectal mucosa) |
| Urinary retention | Not applicable | 1% | 5% (higher risk than TRUS as a result of greater gland swelling) |
| Symptoms associated with general/spinal anaesthetic | Not applicable | Yes | Yes |
| Allergic reaction to contrast medium | Yes but very rare | Not Applicable | Not Applicable |

Procedure related AEs would be expected to occur within 7 days of the procedure.

Whilst there is no obligation to report a serious adverse event (SAE) to the MHRA (as there is no medicinal intervention in the study) the MRC CTU is required to report any SAE that does occur**, and which is deemed related** to **research procedures and unexpected to** the main REC. In order to meet this requirement all study sites are required to report any SAE to MRC CTU within one working day of becoming aware of the event.

The MRC CTU will report to the main REC if the SAE is an untoward and unexpected occurrence that:

a. results in death
b. is life-threatening
c. requires hospitalisation or prolongation of existing hospitalisation
d. results in persistent or significant disability or incapacity
e. consists of a congenital anomaly or birth defect
f. is any other important medical condition

**And** in the opinion of the Chief Investigator (or nominated representative) the event was:

- 'related' – that is, it resulted from administration of any of the research procedures
- 'unexpected' – that is, the type of event is not listed in the protocol as an expected occurrence

Centres should complete the SAE form and fax to 0207 670 4818. The form will be forwarded by the MRC CTU to the Chief Investigator for assessment and reports of related and unexpected SAEs will be submitted within 7 to 15 days of the Chief Investigator becoming aware of the event to main REC.

Any queries about SAE reporting should be directed to the PROMIS Trial Manager.

## SAE NOTIFICATION

**Within one working day of becoming aware of an SAE, please fax a completed SAE form to the MRC Clinical Trials Unit on:**

**Fax: 0207 670 4818**

# 8. QUALITY ASSURANCE & CONTROL OF DATA

## 8.1 Risk assessment

PROMIS is an NCRN-endorsed trial which has undergone independent HTA peer review (expert and consumer representative) and separate reviews by experts on the NIHR HTA committee and the Cancer Group at the MRC CTU.

UCLH and MRC CTU have performed a risk assessment to assess the impact of study participation on the rights and safety of patients, the reliability of the study results and the impact of study results on the site leading the study. This has guided the development of procedures in the study with respect to informed consent, confidentiality and trial monitoring which are recorded in a separate document. It is the view of the Chief Investigator and Trial Management Group that PROMIS is considered to be a low risk study with respect to governance, safety and finance.

## 8.2 Monitoring at MRC CTU

The MRC CTU will conduct day-to-day central monitoring of the study. Data stored at the MRC CTU will be checked for missing or unusual values and checked for consistency within participants over time. If any problems are identified, a data clarification form will be sent to the centre by post or email for checking and confirmation or correction, as appropriate and returned to the CTU. Any data which are changed should be crossed through with a single line so as not to prevent reading the original and initialled and dated on the site copy of the CRF. MRC CTU will send reminders for any overdue and missing data. It is also our intention to monitor centres for data compliance in terms of data quality and CRF return.

A crucial aspect of the central monitoring will be to check the blinding of the results between assessors/assessments. Central monitoring will be carried out in accordance with the MRC CTU working practices for this trial. Please refer to protocol section 6.8, the PROMIS MRI SOP and the PROMIS Combined Biopsy SOP for more detail on blinding procedures.

## 8.3 Clinical site monitoring

Participating investigators should agree to allow study-related monitoring, including audits or ethics committee review by providing direct access to source data/documents as required. Patients' consent for this will be obtained as part of the consent process. Details will be provided in the PROMIS Quality Management and Monitoring Plan.

## 8.4 Data quality control and quality assurance

The data collected will be entered into the study database from the original CRF received from the site. The site will retain a copy of the CRF. If investigator input is required to clarify or correct any missing, ambiguous or inconsistent data, the Data Manager will generate a data query form. The Data Manager will send this form to the study team at the site for completion. When the completed data query form is returned to the MRC CTU, the data on the clinical database will be corrected accordingly.

# 9. STATISTICAL CONSIDERATIONS

In order to recommend that MP-MRI be introduced into the diagnostic pathway for prostate cancer, we require evidence that MP-MRI can do two things.

First, that it correctly identifies a substantial proportion of men who have either no prostate cancer or prostate cancer that is very likely to be clinically insignificant.

Second, that MP-MRI improves the detection rate of clinically significant disease compared to that identified by the current standard, TRUS guided biopsy. If both these test attributes are realised the result will be: fewer biopsies overall but improved detection of clinically important prostate cancer in those men that are likely to benefit from both diagnosis and/or treatment.

PROMIS is adequately powered to measure the precision of MP-MRI specificity to at least 70% (from the lower bound of the 95% confidence interval and assuming MP-MRI has a true specificity of at least 77%) and an increase in sensitivity of MP-MRI by at least 22% (from 48% to 70%) compared to TRUS biopsy.

## 9.1 Outcome Measures

### 9.1.1 Primary

There are two primary outcomes in this trial as both are of fundamental importance to decisions regarding the future use of MP-MRI in the diagnostic pathway for the prostate cancer:

1. Proportion of men who could safely avoid biopsy as determined by specificity and negative predictive values (NPV)
2. Proportion of men correctly identified by MP-MRI to have clinically significant prostate cancer as determined by sensitivity and positive predictive values (PPV)

For the primary outcomes we take DEFINITION ONE (A dominant Gleason pattern ≥ 4 and/or a cancer core length ≥ 6 mm, see section 2.6) as the criteria for clinically significant prostate cancer as assessed by TPM, the most appropriate reference standard.

Alongside these outcomes, the accuracy of TRUS will also be reported in terms of sensitivity, specificity, NPV, and PPV as listed in the section below. In addition, a head-to-head comparison of the sensitivity of MP-MRI versus TRUS guided biopsy (current standard) will be performed amongst men diagnosed with clinically significant prostate cancer according to TPM.

For the primary outcome, a score of 3 or more on MRI will be used to define a potentially clinically significant cancer (see section 6.1 for details). A dominant Gleason pattern ≥ 4 and/or a cancer core length ≥ 6 mm will be used for clinically significant cancer (see DEFINITION ONE section 2.6) for the biopsies.

### 9.1.2 Secondary

- The proportion of men who could safely avoid biopsy, given that they do not have DEFINITION TWO (see section 2.6) prostate cancer as assessed by TPM.

- The proportion of men testing positive on MP-MRI out of those with DEFINITION TWO prostate cancer assessed by TPM.
- Performance characteristics of TRUS versus TPM (sensitivity, specificity, NPV, PPV) according to DEFINITIONS ONE and TWO.
- Evaluation of the optimal combination of MP-MRI functional parameters (T2, DW, DCE) to detect or rule-out clinically significant prostate cancer.
- Intra-observer variability in the reporting of MP-MRI.
- Inter-observer variability in the reporting of MP-MRI.
- Evaluation of socio-demographic, clinical, imaging and radiological variables in relation to the detection of clinically significant prostate cancer.
- Patients' health-related quality of life using the EQ-5D instrument.
- Resource use and costs for further economic evaluation (see Section 10 Cost-effectiveness).
- Translational objectives (see section 2.8).

## 9.2 Sample Size

Power calculations were performed in relation to:

(1) Precision around the estimates for the accuracy of MP-MRI in terms of the primary outcome of sensitivity, and

(2) The head-to-head comparison of the MP-MRI versus TRUS

The largest sample size from (1) and (2) was **714** (as detailed in sections 9.2.2 and 9.2.3) and this was taken as the maximum number of men required to have all 3 tests (MP-MRI, TPM and TRUS biopsy) in this study.

### 9.2.1 Prevalence of clinically significant cancer

For all calculations we have assumed:[12 13 50-52]

- 15% of the study population will have clinically important prostate cancer as detected by the reference standard (TPM) according to DEFINITION ONE (PRIMARY).
- 25% of the study population will have clinically significant prostate cancer as detected by the reference standard (TPM) according to DEFINITION TWO (less stringent definition).

These estimates act as inflation factors for the total number of men required for the study.

### 9.2.2 Precision around the accuracy measures of MP-MRI

All calculations are based on 90% power and 5% significance (2-sided). Specified estimates of sensitivity and specificity are considered realistic based on current unpublished and published literature.[53 54]

#### Specificity of MP-MRI

Assuming a specificity of 77%, in order to demonstrate that the lower 95% confidence interval of specificity is at least 70% or greater, we would require 407 cases of negative or clinically insignificant prostate cancer. This is equivalent to a total of 479 men for DEFINITION ONE and 543 men for DEFINITION TWO.

**Sensitivity of MP-MRI**

Assuming a sensitivity of 75%, in order to demonstrate that the lower 95% confidence interval of sensitivity is at least 60% or greater, we would require 97 cases of clinically significant prostate cancer. This is equivalent to a total of **647** men for DEFINITION ONE and **388** men for DEFINITION TWO.

Since the number of men without clinically significant prostate cancer will be much higher than the number with, the precision for estimating specificity and NPV is much greater.

### 9.2.3 MP-MRI versus TRUS

We have assumed TRUS detects 48% of clinically significant prostate cancer [52] [55] and MP-MRI will detect at least 70% (conservative). Using McNemar's test for paired binary observations,[56] in order to show an absolute increase in the proportion of clinically significant cancers detected of at least 22% (from 48% to 70%) with a power of 90% and a 2-sided alpha of 5%, a total of 107 cases are required. This is equivalent to a total study population of **714** men for DEFINITION ONE, **428** men for DEFINITION TWO.

### 9.2.4 Varying sample size assumptions

It is acknowledged that varying any of sample size assumptions could lead to either a decrease or increase in the required sample size. For illustrative purposes, the effect on the sample size for different assumptions is provided in Appendix V. The McNemar's test assumes that the results of TRUS and MP-MRI are independent. It is perhaps more realistic to assume that cancers detected by TRUS are more likely to be detected by MP-MRI than those missed by TRUS (and vice versa). Taking an example, where there is extremely high agreement between the two methods, and MP-MRI detects almost all cases diagnosed by TRUS (and some additional cancers), then approximately 320 and 192 men are required according to DEFINITION ONE and DEFINITION TWO (See Table A1, Appendix V). Therefore, we consider a total of 714 to be the maximum number of patients required to have all 3 tests (MP-MRI, TPM and TRUS biopsy) for this study. This study has been designed to have as short a time as practical between visits for patients and to minimise drop-out (withdrawal or loss to follow-up). Drop-out is expected to be low. If patients do exit the study after registration, or between the MP-MRI and CPB procedures, then further patients will be recruited so that the target number of patients having all 3 tests is maintained.

An independent review of all the sample size assumptions will be made following completion of the pilot study and during the course of the main trial. This will ensure that the optimum sample size is achieved to answer the objectives of this protocol. This will be done without compromising the integrity of the study while minimising the number of men undergoing the combined prostate biopsy procedure.

## 9.3 Analysis plan

Full details of all analyses to be performed will be detailed in the Statistical Analysis Plan (SAP) and reporting of results will following the STARD (STAndards for the Reporting of Diagnostic accuracy studies) practice.

### 9.3.1 Pilot study

**Safety**

The pilot study data will provide an estimate of the rate of sepsis (requiring hospitalisation) following the CPB procedure with ongoing monitoring for safety (as detailed in section 7.1).

**Recruitment rate**

The pilot study will also inform recruitment rate for the main study. The pilot is expected to recruit 50 patients from two centres over one year (which translates to approximately two men per centre per month). The main phase aims to recruit up to 714 men to have MP-MRI and the CPB procedure over an additional 2 to 3 years (approximately two to five men per centre per month).

The internal pilot data will also contribute to the main analyses and the recruitment rate should adequately account for start-up time across centres.

**Preliminary cost-effectiveness modelling**

A preliminary economic model based on existing sources of evidence will be developed. This will allow assessment of the key uncertainties in the cost-effectiveness of the new diagnostic pathway. This will inform the design of the main phase. See Section 10 for more details.

### 9.3.2 Primary analysis of the main study

The primary analysis will be based on all evaluable data, excluding men without all three test results and any data rejected as part of the external MP-MRI QC/QA process (see section 6.6.1).

The sensitivities, specificities and predictive values will be calculated for MP-MRI based on the overall cancer score for MP-MRI and DEFINITION ONE for clinically significant cancer on TPM biopsy. Results will be presented in a 2 by 2 table (as shown below in Table 4) and estimates will be presented together with 95% confidence intervals (CI).

**Table 4: 2 by 2 tables to demonstrate accuracy of MP-MRI with respect to TPM**

| | | MP-MRI | | |
|---|---|---|---|---|
| | | **+ve** | **-ve** | **Total** |
| **TPM** | **+ve** | a | b | a+b |
| | **- ve** | c | d | c+d |
| | **Total** | a+c | b+d | |

**Specificity = d / (c+d)** where, d = number of men testing negative on MP-MRI and negative for clinically significant cancer on TPM, c = number of men testing positive on MP-MRI who do not have clinically significant cancer on TPM.

**Negative Predictive Value (NPV) = d / (b+d)** where, d = number of men testing negative on MP-MRI and negative for clinically significant cancer on TPM, b= number of men testing negative on MP-MRI who have clinically significant cancer on TPM.

**Sensitivity = a / (a+b)** where, a = number of men testing positive on MP-MRI and positive for clinically significant on TPM, b = number of men testing negative for MP-MRI who have clinically significant cancer on TPM.

**Positive Predictive Value (PPV) = a / (a+c)** where, a = number of men testing positive on MP-MRI and positive for clinically significant on TPM, c = number of men testing positive on MP-MRI who do not have clinically significant cancer on TPM.

**Comparison of TRUS guided biopsy and MP-MRI:** McNemar's test will be used to compare the agreement between MP-MRI and TRUS biopsies in the subset of men found to have clinically significant prostate cancer according to DEFINITION ONE. Results will be presented in a 2 by 2 table as shown below in Table 5.

**Table 5: 2 by 2 table demonstrating the comparison of TRUS guided biopsy and MP-MRI**

| | | MP-MRI | | |
|---|---|---|---|---|
| | | **+ve** | **-ve** | **Total** |
| **TRUS** | **+ve** | r | s | r+s |
| | **- ve** | t | u | t+u |
| | **Total** | r+t | s+u | Npairs |

### 9.3.3 Secondary analysis of the main study

1. All analyses performed for DEFINITION ONE (primary analysis) will be repeated for DEFINITION TWO.

2. The sensitivity, specificity and predictive values of MP-MRI will be presented (according to DEFINITIONS ONE and TWO) for each of the 12 ROI (see section 6.1). Agreement between the MP-MRI and TPM in identifying clinically significant cancer in the same region will be based on a nearest neighbourhood approach.[57] Sensitivity to this approach will be tested by also presenting results according to complete match (most stringent rule) and using a left/right rule (less stringent rule).

3. The sensitivity, specificity and predictive values of MP-MRI will be presented (according to DEFINITIONS ONE and TWO) for each of the individual MRI reporting sequence combinations, namely T2, T2+DW and T2+DW+DCE.

4. Inter-observer reliability: Coefficients of reliability will be derived to determine intra-observer and inter-observer reliability. Although the local radiologist will report all images from their centre, the pilot data (and a sample from the main study as required) will be used to evaluate reliability, so as to reduce the burden on reporters that would result if all reporters had to assess each scan twice. All MRI assessments in the pilot will be randomly re-allocated to five central radiologists in equal numbers for re-assessment. The radiologists will perform the re-assessments blind to the results of the first assessment and first examiner. A proportion of MRI scans will therefore be re-examined by the same examiner.[58] In the main phase, at least a proportion of MRI assessments will be randomly re-allocated to one of five other radiologists for re-assessment to be reported blind to any previous assessments or histology. None will be blinded to clinical details (i.e. PSA and DRE findings).

# 10. COST-EFFECTIVENESS

## 10.1 Introduction

Two important health economic consequences arise from the current diagnostic pathway. First, many men receive a diagnosis of a clinically insignificant prostate cancer and, as a result, have treatment that is unlikely to confer benefit (over-diagnosis/over-treatment). Second, men with clinically significant disease are routinely missed. Inclusion of MRI into the pathway has the potential to reduce both errors. Reduction in the rate of occurrence of these errors is likely to result in overall health gain and possibly reduced NHS costs. The economic considerations of altering the current diagnostic pathway constitute one of our primary objectives.

## 10.2 Economic analysis

### 10.2.1 Pilot study

During the pilot phase of the project an initial cost-effectiveness model will be developed. This model will be populated from the pilot study as well as a review of secondary sources of epidemiological, clinical and economic evidence together with appropriately elicited expert opinion.[59] The use of probabilistic sensitivity analysis, value of information methods and scenario analysis [60] will quantify the uncertainty associated with identifying the most cost effective diagnostic strategy, the costs of that uncertainty (in health and resource terms) and the key uncertainties to resolve with further research. This will inform the inputs into the main economic model. This preliminary cost-effectiveness model will seek to quantify the long-term implication of changes to the diagnostic classification of prostate cancer that result from adoption of alternative diagnostic pathways within the NHS. The implications will relate to the health effects (in terms of quality adjusted life expectancy) and NHS costs of a given diagnostic pathway placing patients into each of the four groups:

1. MRI test positive, clinically significant disease
2. MRI test negative, clinically significant disease
3. MRI test positive, clinically insignificant disease
4. MRI test negative, clinically insignificant disease

Clinically significant cancer will be specified by DEFINITIONS ONE and TWO on TPM biopsy. By altering the likelihood of a man falling into any one of these groups, the value of MP-MRI will be assessed by the changes in average outcomes experienced by men and the costs that result. The model will also include the implications of a positive result in the index test concurrent with a negative result in the current standard as well as accounting for the side effect profile of different diagnostic pathways. Structurally, the model will consist of a diagnostic element which will model the probabilities of a given patient falling into each of the diagnostic groups above, and a prognostic element which will estimate the long term implications for health and costs. The specific details of model structure will be informed by a review of existing prostate cancer models including those relating to screening, diagnosis and treatment. In general terms the modelling will adhere to the methods advocated to inform guidance by the National Institute for Health and Clinical Excellence.[61] The preliminary modelling will indicate the main sources of uncertainty associated with the cost-effectiveness of the new pathway. This will inform the final design of main study including the selection of endpoints with respect to this primary objective.

The main phase of the project will provide estimates of key clinical, economic and epidemiological inputs for the model. The most important of these is likely to be the accuracy of the alternative tests (which facilitate estimates of the likelihood of falling into the diagnostic groups detailed above). However, the main phase of the project will also provide a vehicle for the collection of other relevant data to inform cost-effectiveness. These will include the costs of tests and the management of adverse events, and the health-related quality of life (HRQL) implications of any adverse events experienced with tests. The latter will be assessed using the EQ-5D instrument (see Appendix III) as part of the main clinical study. This is a widely used generic measure of HRQL which can be used to derive quality adjusted life years (QALYs).[62] On completion of the data collection for the main phase, the evidence synthesis and modelling undertaken in the first phase will be updated, and the evidence collected in the main study added to it. Ultimately, this work will provide an assessment of the implications of any change that the use of MP-MRI has on under-detection and over-detection. These implications will be in terms of expected quality adjusted survival duration and long-term health service costs. This will allow the value for money of MP-MRI in this context to be assessed using the same metrics employed to evaluate therapeutic technologies by organisations such as NICE.

# 11. ETHICAL CONSIDERATIONS AND APPROVAL

## 11.1 Ethical considerations

Patients agreeing to participate in this study will all receive exactly the same procedures and must be willing to accept the implications these procedures may have. Two lay persons Robert Oldroyd (Prostate Cancer Charity Research Advisory Committee & Nottingham 1 Research Ethics Committee) and Stewart Robinson (Nottingham Prostate Support Group) helped the study team to ensure that the benefits for the men in the study are significant and the risks are minimal. In addition, the protocol, consent form and patient information sheet have been reviewed by a patient representative, Richard Stephens (Lymphoma CSG Sub-Groups, NCRI's Strategic Consumer Involvement Steering Group & NCRN Consumer Liaison Group), who took part in the internal review process at the MRC Clinical Trials Unit.

The study will abide by the principles of the Declaration of Helsinki and the UK Research Governance Framework version 2.

## 11.2 Risks and benefits of study procedures

To confirm whether or not MP-MRI can detect clinically significant prostate cancer it is necessary to expose men to a test that can verify the presence or the absence of clinically significant disease. The only test that can reliably do this is TPM. TPM is done under general/spinal anaesthetic and takes about 30-40 minutes to perform. In contrast, TRUS guided biopsies are carried out under local anaesthetic and take 15 minutes to perform. It is noted that men are being asked to go through a more extensive set of biopsies. However, a number of collaborating centres currently offer either TRUS guided biopsies and TPM to men.

The whole MP-MRI scan takes about 30 to 40 minutes. MP-MRI rarely has any side effects. Some men find the scanner claustrophobic. Putting a cannula in the arm which is used to inject the contrast agent may cause mild discomfort and, rarely, nausea and vomiting (less than 5 in 10,000 people). Very rarely the contrast agent may cause an allergic reaction. Such reactions are usually mild. A severe allergic reaction will occur in less than 1 in 10,000 people.

TPM alone has a reduced risk of infection and sepsis; there is little to no rectal bleeding; and there is little to no pain as they are done under general/spinal anaesthetic. The main disadvantage is that it is associated with an increased risk of failure to void urine. In such a case a temporary catheter is placed into the bladder overnight and removed the following day. This occurs in about 1 in 20 men with TPM as opposed to 1 in 100 men having TRUS guided biopsies. It is not anticipated that this poses significant additive risk, as other groups have carried out both TRUS biopsies and transperineal biopsies at the same sitting with no extra morbidity.[63 64] However, the internal pilot will provide data regarding the safety of this combined procedure.

Men taking part in the study will have a general/spinal, rather than a local anaesthetic and a larger number of biopsy cores than in standard clinical practice. However, there are also benefits to patients taking part in the study:

1. Greater diagnostic accuracy from more comprehensive sampling of the prostate conferring more precise risk stratification

2. Less discomfort during the biopsy because of the anaesthetic. In addition, for those men diagnosed as having prostate cancer, timely staging information will be available from a high quality MP-MRI that is free of biopsy artefact

The patient information sheet clearly describes the risks and disadvantages to the patient of participating in this study.

## 11.3 Ethical approval

The protocol and each participating centre will have Research Ethics Committee approval before patients are entered. Copies of the documents listed in Section 3 must be sent to the MRC CTU before registering patients.

The patient's consent to participate in the study should be obtained after a full explanation has been provided of the procedures to be given. Patients should be given sufficient time (at least 24 hours) after being given the study patient information sheet to consider and discuss participation in the study with family and friends. A contact number will be given to the patient should he wish to discuss any aspect of the study. Following this, the clinician will determine that the patient is fully informed of the study and their participation, in accordance with ICH GCP guidelines. Patients will always be asked to sign a consent form. One copy will be given to the patient, one copy will be kept with patient's hospital notes and one copy should be kept in the local investigator's file.

The right of the patient to refuse to participate in the study without giving reasons must be respected. After the patient has entered the study, the clinician must remain free to manage the patient however he/she feels fit to suit the best interest of the patient, regardless of the protocol. Similarly, the patient must remain free to withdraw from the study at any time without giving reasons and without prejudicing any further treatment or the standard of care received.

A statement of MRC policy on ethical considerations in clinical trials on cancer therapy, including the question of informed consent, is available from the MRC Head Office web site (http://www.mrc.ac.uk). This may be used to give guidance to participating investigators and to accompany ethics applications.

# 12. REGULATORY ISSUES

University College London is the UK research governance sponsor of PROMIS and has delegated roles and responsibilities for trial management, data management and analyses to the MRC CTU.

This is not a Clinical Trial of an Investigational Medicinal Product (IMP) as defined by the EU Directive 2001/20/EC. Therefore, a Clinical Trial Authorisation (CTA) is not required.

The study will be conducted in accordance with the principles of GCP, as represented in the MRC GCP guidelines, and UK Research Governance Framework guidelines, version 2, will be strictly adhered to.

# 13. INDEMNITY

University College London holds insurance against claims from participants for injury caused by their participation in this clinical study. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, if this clinical study is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical study. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

Hospitals selected to participate in this study must provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary can be provided on request.

# 14. FINANCE

PROMIS has public funding from the National Institute for Health Research, Health Technology Assessment (NIHR HTA) programme. Research funding is provided for the joint conduct of the study by UCL & the CTU as well as radiology and pathology reporting time.

# 15. TRIAL COMMITTEES

## 15.1 Trial Management Group (TMG)

A Trial Management Group (TMG) will be responsible for the day-to-day running and management of the trial and will provide clinical advice and support. The TMG will operate in accordance with a trial-specific charter which will detail the TMG roles, functions and membership. All members of the TMG will be expected to sign the TMG charter.

The TMG will consist, as a minimum, of the chief investigator(s), at least one of the Co-PIs, the CTU Project Lead, the trial statistician and the trial manager. The TMG, collaborating clinicians and CTU staff will promote the trial through national and international meetings, newsletters, patient-advocacy groups, and (where suitable) the media. They will encourage compliance and sustain interest by the same means and through visits to collaborating centres.

## 15.2 Trial Steering Committee (TSC)

The MRC CTU Urological and Lung Cancer Trial Steering Committee will carry out an independent review of the protocol prior to study initiation and perform planned reviews of pilot and main study. There is no separate IDMC for this non-CTIMP study as the TSC will also perform safety and data monitoring.

The TSC has independent members, including an independent Chair, and it can draw on members of the TMG for the purposes of discussion. The TSC membership may be supplemented for the purposes of this trial, for example experts in microbiology, radiology and/or pathology may be invited to advise on specific issues that arise. The TSC will provide overall supervision for the trial and advice through its independent Chair. The ultimate decision for the continuation of the trial lies with the TSC. Further details of TSC functioning are presented in the TSC Charter, available from the MRC CTU. All members of the TSC will be expected to sign the TSC charter.

The TSC, along with UCL as sponsor, will review and approve, via a formal process, applications to use data or samples collected in PROMIS. This would include translational research, whether entirely academic or to be carried out in conjunction with a commercial entity. It would also include research proposals requiring future ethical approval such as potential long-term follow up of PROMIS participants via questionnaires.

# 16. PUBLICATION

The results from different centres will be analysed together and published as soon as possible and is appropriate. All study-related communications can only be presented or published after approval from the TMG. The TMG will form the basis of the writing committee for the primary publications and will advise on the publication of any related reports.

All publications shall include appropriate indication of the PROMIS investigator team and any requirement for named authors will be proposed by the TMG. For the main study reports, senior and first authorship will be determined by agreement of the Chief Investigator, the co-PIs and the CTU leads, at time of manuscript drafting. If there are no named authors (i.e. group authorship) then a writing committee will be identified that would usually include these people. The clinical trials.gov registration number that has been allocated to this trial will be attached to any publications resulting from this trial.

The members of the TSC will be listed with their affiliations in the acknowledgements/appendix of the main publication.

# 17. PROTOCOL AMENDMENTS

## First amendment

The PROMIS protocol was amended in July 2011. The following changes were made;

- Updated contact details.
- Removed 'Copy of Site specific approval from ethics' from Section 3 Selection of Centres/Clinicians.
- Updated inclusion criteria to included 'Men at least 18 years or over at risk of prostate cancer who have been advised to have a prostate biopsy'.
- Changed the order of exclusion criteria.
- Clarifications to pre-registration investigations
- Updated overall prostate score.
- Removed 'fractional anisotropy values' from Section 6.1 Visit 2: MP-MRI.
- Updated data collection timelines and added CPB Procedure Checklist and Withdrawal Form.
- Updated the wording of Section 6.10 Withdrawal.
- Removed sentence about 'accredited sites will be supplied with a partially completed SAE form'.

## Second Amendment

The PROMIS protocol was amended in February 2012. The following changes were made;

• Minor corrections to typographical errors throughout the protocol have been made.

• Correction of contact details.

• Inclusion of ISRCTN number.

• Patient exclusion criteria clarified.

• Clarifications to pre-registration investigations.

• Changed name of Basingstoke and North Hampshire Foundation Trust to North Hampshire Hospitals NHS trust.

• Trial schema slightly amended

• Process to be followed by pathologists clarified.

# REFERENCES


1. Cancer Research UK, Cancer Statistics, 2006.
2. Andriole GL, Crawford ED, Grubb RL, 3rd, Buys SS, Chia D, Church TR, et al. Mortality results from a randomized prostate-cancer screening trial. *N Engl J Med* 2009;360(13):1310-9.
3. Hugosson J, Carlsson S, Aus G, Bergdahl S, Khatami A, Lodding P, et al. Mortality results from the Goteborg randomised population-based prostate-cancer screening trial. *Lancet Oncol*;11(8):725-32.
4. Schroder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V, et al. Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med* 2009;360(13):1320-8.
5. Barry MJ. Screening for prostate cancer--the controversy that refuses to die. *N Engl J Med* 2009;360(13):1351-4.
6. Parker C, Emberton M. Screening for prostate cancer appears to work, but at what cost? *BJU Int* 2009;104(3):290-2.
7. Bossuyt PM, Irwig L, Craig J, Glasziou P. Comparative accuracy: assessing new tests against existing diagnostic pathways. *Bmj* 2006;332(7549):1089-92.
8. Prostate Cancer: Diagnosis and Treatment: National Institute for Health and Clinical Excellence (NICE). Feb 2008. ISBN 978-0-9558265-0-4. National Collaborating Centre for Cancer (NCC-C).
9. Kelloff GJ, Choyke P, Coffey DS. Challenges in clinical prostate cancer: role of imaging. *AJR Am J Roentgenol* 2009;192(6):1455-70.
10. Thompson IM, Goodman PJ, Tangen CM, Lucia MS, Miller GJ, Ford LG, et al. The influence of finasteride on the development of prostate cancer. *N Engl J Med* 2003;349(3):215-24.
11. Bangma CH, Roemeling S, Schroder FH. Overdiagnosis and overtreatment of early detected prostate cancer. *World J Urol* 2007;25(1):3-9.
12. Djavan B, Ravery V, Zlotta A, Dobronski P, Dobrovits M, Fakhari M, et al. Prospective evaluation of prostate cancer detected on biopsies 1, 2, 3 and 4: when should we stop? *J Urol* 2001;166(5):1679-83.
13. Scattoni V, Zlotta A, Montironi R, Schulman C, Rigatti P, Montorsi F. Extended and saturation prostatic biopsy in the diagnosis and characterisation of prostate cancer: a critical analysis of the literature. *Eur Urol* 2007;52(5):1309-22.
14. Kulkarni GS, Al-Azab R, Lockwood G, Toi A, Evans A, Trachtenberg J, et al. Evidence for a biopsy derived grade artifact among larger prostate glands. *J Urol* 2006;175(2):505-9.
15. Kurhanewicz J, Vigneron D, Carroll P, Coakley F. Multiparametric magnetic resonance imaging in prostate cancer: present and future. *Curr Opin Urol* 2008;18(1):71-7.
16. Kirkham AP, Emberton M, Allen C. How good is MRI at detecting and characterising cancer within the prostate? *Eur Urol* 2006;50(6):1163-74; discussion 1175.
17. Ahmed HU, Kirkham A, Arya M, Illing R, Freeman A, Allen C, et al. Is it time to consider a role for MRI before prostate biopsy? *Nat Rev Clin Oncol* 2009;6(4):197-206.
18. Bernstein MR, Cangiano T, D'Amico A, Chittams J, Hardy C, Whittington RD, et al. Endorectal coil magnetic resonance imaging and clinicopathologic findings in T1c adenocarcinoma of the prostate. *Urol Oncol* 2000;5(3):104-107.
19. Cornud F, Flam T, Chauveinc L, Hamida K, Chretien Y, Vieillefond A, et al. Extraprostatic spread of clinically localized prostate cancer: factors predictive of pT3 tumor and of positive endorectal MR imaging examination results. *Radiology* 2002;224(1):203-10.
20. May F, Treumann T, Dettmar P, Hartung R, Breul J. Limited value of endorectal magnetic resonance imaging and transrectal ultrasonography in the staging of clinically localized prostate cancer. *BJU Int* 2001;87(1):66-9.
21. Outwater EK, Petersen RO, Siegelman ES, Gomella LG, Chernesky CE, Mitchell DG. Prostate carcinoma: assessment of diagnostic criteria for capsular penetration on endorectal coil MR images. *Radiology* 1994;193(2):333-9.
22. Rifkin MD, Zerhouni EA, Gatsonis CA, Quint LE, Paushter DM, Epstein JI, et al. Comparison of magnetic resonance imaging and ultrasonography in staging early prostate cancer. Results of a multi-institutional cooperative trial. *N Engl J Med* 1990;323(10):621-6.
23. Schiebler ML, Yankaskas BC, Tempany C, Spritzer CE, Rifkin MD, Pollack HM, et al. MR imaging in adenocarcinoma of the prostate: interobserver variation and efficacy for determining stage C disease. *AJR Am J Roentgenol* 1992;158(3):559-62; discussion 563-4.
24. Schnall MD, Pollack HM. Magnetic resonance imaging of the prostate gland. *Urol Radiol* 1990;12(2):109-14.
25. Chen M, Dang HD, Wang JY, Zhou C, Li SY, Wang WC, et al. Prostate cancer detection: comparison of T2-weighted imaging, diffusion-weighted imaging, proton magnetic resonance spectroscopic imaging, and the three techniques combined. *Acta Radiol* 2008;49(5):602-10.
26. Futterer JJ, Heijmink SW, Scheenen TW, Veltman J, Huisman HJ, Vos P, et al. Prostate cancer localization with dynamic contrast-enhanced MR imaging and proton MR spectroscopic imaging. *Radiology* 2006;241(2):449-58.

27. Kozlowski P, Chang SD, Jones EC, Berean KW, Chen H, Goldenberg SL. Combined diffusion-weighted and dynamic contrast-enhanced MRI for prostate cancer diagnosis--correlation with biopsy and histopathology. *J Magn Reson Imaging* 2006;24(1):108-13.
28. Kumar V, Jagannathan NR, Kumar R, Das SC, Jindal L, Thulkar S, et al. Correlation between metabolite ratios and ADC values of prostate in men with increased PSA level. *Magn Reson Imaging* 2006;24(5):541-8.
29. Macura KJ. Multiparametric magnetic resonance imaging of the prostate: current status in prostate cancer detection, localization, and staging. *Semin Roentgenol* 2008;43(4):303-13.
30. Mazaheri Y, Shukla-Dave A, Hricak H, Fine SW, Zhang J, Inurrigarro G, et al. Prostate cancer: identification with combined diffusion-weighted MR imaging and 3D 1H MR spectroscopic imaging--correlation with pathologic findings. *Radiology* 2008;246(2):480-8.
31. Noworolski SM, Henry RG, Vigneron DB, Kurhanewicz J. Dynamic contrast-enhanced MRI in normal and abnormal prostate tissues as defined by biopsy, MRI, and 3D MRSI. *Magn Reson Med* 2005;53(2):249-55.
32. Reinsberg SA, Payne GS, Riches SF, Ashley S, Brewster JM, Morgan VA, et al. Combined use of diffusion-weighted MRI and 1H MR spectroscopy to increase accuracy in prostate cancer detection. *AJR Am J Roentgenol* 2007;188(1):91-8.
33. Tanimoto A, Nakashima J, Kohno H, Shinmoto H, Kuribayashi S. Prostate cancer screening: the clinical value of diffusion-weighted imaging and dynamic MR imaging in combination with T2-weighted imaging. *J Magn Reson Imaging* 2007;25(1):146-52.
34. van Dorsten FA, van der Graaf M, Engelbrecht MR, van Leenders GJ, Verhofstad A, Rijpkema M, et al. Combined quantitative dynamic contrast-enhanced MR imaging and (1)H MR spectroscopic imaging of human prostate cancer. *J Magn Reson Imaging* 2004;20(2):279-87.
35. Yoshimitsu K, Kiyoshima K, Irie H, Tajima T, Asayama Y, Hirakawa M, et al. Usefulness of apparent diffusion coefficient map in diagnosing prostate carcinoma: correlation with stepwise histopathology. *J Magn Reson Imaging* 2008;27(1):132-9.
36. Harlan SR, Cooperberg MR, Elkin EP, Lubeck DP, Meng MV, Mehta SS, et al. Time trends and characteristics of men choosing watchful waiting for initial treatment of localized prostate cancer: results from CaPSURE. *J Urol* 2003;170(5):1804-7.
37. Ahmed HU, Calleary J, Arya M, Emberton M, Illing RO, Allen C. Re: Dynamic contrast enhanced, pelvic phased array magnetic resonance imaging of localized prostate cancer for predicting tumor volume: correlation with radical prostatectomy findings. A. Villers, P. Puech, D. Mouton, X. Leroy, C. Ballereau and L. Lemaitre, J Urol 2006; 176: 2432-2437. *J Urol* 2007;177(6):2395; author reply 2395-6.
38. Onik G, Miessau M, Bostwick DG. Three-dimensional prostate mapping biopsy has a potentially significant impact on prostate cancer management. *J Clin Oncol* 2009;27(26):4321-6.
39. Barzell WE, Melamed MR. Appropriate patient selection in the focal treatment of prostate cancer: the role of transperineal 3-dimensional pathologic mapping of the prostate--a 4-year experience. *Urology* 2007;70(6 Suppl):27-35.
40. Li H, Yan W, Zhou Y, Ji Z, Chen J. Transperineal ultrasound-guided saturation biopsies using 11-region template of prostate: report of 303 cases. *Urology* 2007;70(6):1157-61.
41. Merrick GS, Taubenslag W, Andreini H, Brammer S, Butler WM, Adamovich E, et al. The morbidity of transperineal template-guided prostate mapping biopsy. *BJU Int* 2008;101(12):1524-9.
42. Onik G, Barzell W. Transperineal 3D mapping biopsy of the prostate: an essential tool in selecting patients for focal prostate cancer therapy. *Urol Oncol* 2008;26(5):506-10.
43. Bott SR, Henderson A, Halls JE, Montgomery BS, Laing R, Langley SE. Extensive transperineal template biopsies of prostate: modified technique and results. *Urology* 2006;68(5):1037-41.
44. Crawford ED, Wilson SS, Torkko KC, Hirano D, Stewart JS, Brammell C, et al. Clinical staging of prostate cancer: a computer-simulated study of transperineal prostate biopsy. *BJU Int* 2005;96(7):999-1004.
45. Furuno T, Demura T, Kaneta T, Gotoda H, Muraoka S, Sato T, et al. Difference of cancer core distribution between first and repeat biopsy: In patients diagnosed by extensive transperineal ultrasound guided template prostate biopsy. *Prostate* 2004;58(1):76-81.
46. Buskirk SJ, Pinkstaff DM, Petrou SP, Wehle MJ, Broderick GA, Young PR, et al. Acute urinary retention after transperineal template-guided prostate biopsy. *Int J Radiat Oncol Biol Phys* 2004;59(5):1360-6.
47. Miller J, Perumalla C, Heap G. Complications of transrectal versus transperineal prostate biopsy. *ANZ J Surg* 2005;75(1-2):48-50.
48. Transperineal template biopsy and mapping of the prostate: National Institute for Health and Clinical Excellence (NICE). October 2010. ISBN 978-0-84936-381-5.
49. Barzell W. Personal communication. 2010.
50. Dall'Era MA, Cooperberg MR, Chan JM, Davies BJ, Albertsen PC, Klotz LH, et al. Active surveillance for early-stage prostate cancer: review of the current literature. *Cancer* 2008;112(8):1650-9.

51. Djavan B, Milani S, Remzi M. Prostate biopsy: who, how and when. An update. *Can J Urol* 2005;12 Suppl 1:44-8; discussion 99-100.

52. Taira AV, Merrick GS, Galbreath RW, Andreini H, Taubenslag W, Curtis R, et al. Performance of transperineal template-guided mapping biopsy in detecting prostate cancer in the initial and repeat biopsy setting. *Prostate Cancer Prostatic Dis* 2010;13(1):71-7.

53. Lim HK, Kim JK, Kim KA, Cho KS. Prostate cancer: apparent diffusion coefficient map with T2-weighted images for detection--a multireader study. *Radiology* 2009;250(1):145-51.

54. Turkbey B, Thomasson D, Pang Y, Bernardo M, Choyke PL. The role of dynamic contrast-enhanced MRI in cancer diagnosis and treatment. *Diagn Interv Radiol* 2010;16(3):186-92.

55. Eichler K, Hempel S, Wilby J, Myers L, Bachmann LM, Kleijnen J. Diagnostic value of systematic biopsy methods in the investigation of prostate cancer: a systematic review. *J Urol* 2006;175(5):1605-12.

56. Machin D, Campbell MJ, Tan SB, Tan SH. *Sample Size Tables for Clinical Studies*. Third ed: Wiley-Blackwell, 2009.

57. Turkbey B, Pinto PA, Mani H, Bernardo M, Pang Y, McKinney YL, et al. Prostate cancer: value of multiparametric MR imaging at 3 T for detection--histopathologic correlation. *Radiology* 2010;255(1):89-99.

58. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;1(8476):307-10.

59. O'Hagan A, Buck CE, Bdaneshkhah A, Eiser JR, Garthwaite PH, Jenkinson DJ, et al. *Uncertain Judgements: Eliciting Experts' Probabilities*. Chichester: John Wiley and Sons Ltd, 2006.

60. Briggs A, Claxton K, Schulpher M. *Decision Modelling for Health Economic Evaluation*. Oxford: Oxford University Press, 2006.

61. National Institute for Health and Clinical Excellence (NICE). Guide to Methods of Technology Appraisal. London: NICE, 2008.

62. Kind P, Spilker B. The EuroQoL instrument: an index of health-related quality of life. *Quality of Life and Pharmacoeconomics in Clinical Trials*. Philadelphia: Lippincott-Raven, 1996:191-201.

63. Hara R, Jo Y, Fujii T, Kondo N, Yokoyoma T, Miyaji Y, et al. Optimal approach for prostate cancer detection as initial biopsy: prospective randomized study comparing transperineal versus transrectal systematic 12-core biopsy. *Urology* 2008;71(2):191-5.

64. Numao N, Kawakami S, Yonese J, Koga F, Saito K, Fujii Y, et al. Three-dimensional 26-core biopsy-based patient selection criteria for nerve-sparing radical prostatectomy. *Int J Urol* 2008;15(12):1061-6.

# APPENDICES

Please refer to PROMIS Protocol Appendices

# PROMIS
# Prostate MRI Imaging Study

Evaluation of Multi-Parametric Magnetic Resonance Imaging in the Diagnosis and Characterisation of Prostate Cancer

**Developed with the NCRI Prostate Clinical Studies Group**

ISRCTN: 16082556
MRC: PR11
UCL reference number: 11/0009
REC reference: 11/LO/0185

**Part of the NIHR National Cancer Research Network Portfolio**

## Protocol Appendices Version 3.0

**02nd February 2012**

**Authorised by:**

| | | |
|---|---|---|
| **Name** | **Prof Mark Emberton** | **Signature:** |
| Role | Chief Investigator | Date: 02nd February 2012 |
| **Name** | **Dr Rhian Gabe** | **Signature:** |
| Role | Project Lead, CTU | Date: 02nd February 2012 |

## APPENDICES

# APPENDIX I: MAIN TYPES OF MR IMAGES

## T2 Weighting (T2)

Prostate cancer is characterised by a relatively low T2 signal when compared to normal peripheral zone tissue. However, the presence of reduced T2 signal in the peripheral zone is of limited sensitivity (approximately 60%) because some tumours are iso-intense.[1] In addition, the tissue changes that result from both prostate biopsy and the pathological processes of prostatitis, atrophy and hyperplasia can mimic prostate cancer in the peripheral zone.[2 3] The false positives that result mean that the specificity is usually below 50%.

## Diffusion Weighting (DW)

DW provides image contrast by averaging the diffusion properties of water within tissues. Cancers tend to have higher cell densities and a greater ratio of membrane to water. As a result, water diffuses less rapidly in cancer compared to non-cancer for any given tissue type.[4 5] DW images take about 5 minutes to acquire. The images discriminate cancer from non-cancer with high resolution. Studies combining T2 Weighting and DW for localising prostate cancer, show that sensitivity in the detection of significant cancer within the peripheral zone increased when compared with T2 Weighting alone.[6 7] Studies have shown the sensitivity to be 71-87% and specificity 61-89%.[6-12] DW may also provide prediction of tumour aggressiveness.[13]

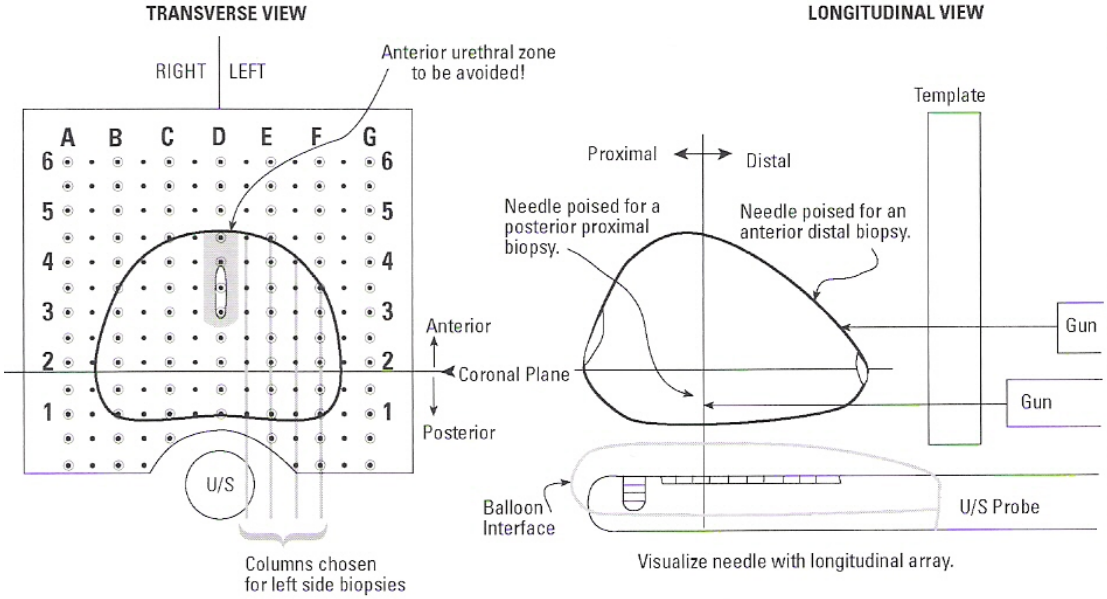
## Dynamic Contrast Enhancement (DCE)

Fast T1-weighted DCE results in good spatial resolution and has been used to study tumour blood supply. It is performed by injecting a bolus of low molecular-weight MR contrast agent (gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA)) intravenously and acquiring a rapid series of images over a short period of time (7-10 min). DCE can discriminate prostate cancer from surrounding healthy prostate tissue based on a higher and faster rate of contrast enhancement.[14] Recently, one group used DCE on a 1.5 Tesla scanner using a pelvic-phased array prior to prostate biopsy in men with a raised PSA. The sensitivity, specificity, positive and negative predictive values for DCE in cancer detection were 77%, 91%, 86% and 85% for foci greater than 0.2ml, and 90%, 88%, 77% and 95% for foci greater than 0.5ml, respectively, with respect to whole-mount radical prostatectomy histology.[15]

# APPENDIX II: TEMPLATE PROSTATE MAPPING PROTOCOL

A brachytherapy template is placed over the perineum (Figure A1). The prostate can be visualised on ultrasound with a grid superimposed; each coordinate representing a grid hole. Biopsy needles are inserted at each hole in which prostate tissue is found. If the prostate is longer than the biopsy needle then two deployments of the needle are necessary (right lower Gun and arrow, Figure A1).

**Figure A1: Template Prostate Mapping Protocol**



# APPENDIX III: HEALTH ECONOMICS: EQ-5D

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

**Mobility**

| | |
|---|---|
| I have no problems in walking about | ❑ |
| I have some problems in walking about | ❑ |
| I am confined to bed | ❑ |

**Self-Care**

| | |
|---|---|
| I have no problems with self-care | ❑ |
| I have some problems washing or dressing myself | ❑ |
| I am unable to wash or dress myself | ❑ |

**Usual Activities** (*e.g. work, study, housework, family or leisure activities)*

| | |
|---|---|
| I have no problems with performing my usual activities | ❑ |
| I have some problems with performing my usual activities | ❑ |
| I am unable to perform my usual activities | ❑ |

**Pain / Discomfort**

| | |
|---|---|
| I have no pain or discomfort | ❑ |
| I have moderate pain or discomfort | ❑ |
| I have extreme pain or discomfort | ❑ |

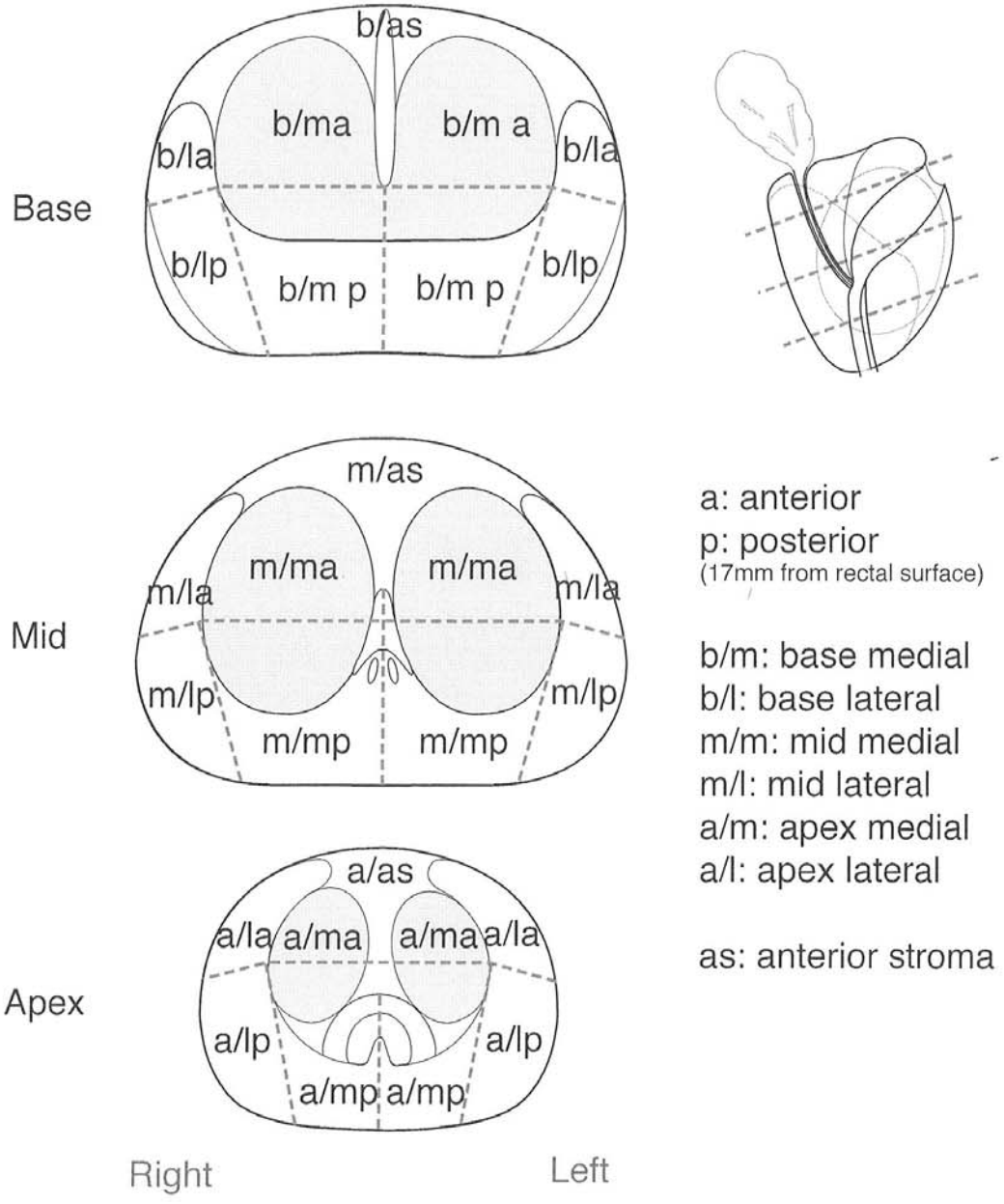
**Anxiety / Depression**

| | |
|---|---|
| I am not anxious or depressed | ❑ |
| I am moderately anxious or depressed | ❑ |
| I am extremely anxious or depressed | ❑ |

# APPENDIX IV: 27 REGIONS OF INTEREST OF PROSTATE

Imaging - biopsy - pathology standardized report

27 sectors scheme
12 posterior - 12 anterior - 3 anterior stroma




a: anterior
p: posterior
(17mm from rectal surface)

b/m: base medial
b/l: base lateral
m/m: mid medial
m/l: mid lateral
a/m: apex medial
a/l: apex lateral

as: anterior stroma

# APPENDIX V: IMPACT ON SAMPLE SIZE OF VARIATIONS IN ASSUMPTIONS

**Table A1: Required sample size for McNemar test for different levels of agreement between MP-MRI and TRUS**

| | TRUS result (for true cases)* | | | | Required number of cases** | Required sample size | |
|---|---|---|---|---|---|---|---|
| | Negative | | Positive | | | | |
| MF-MRI results | Negative | Positive | Negative | Positive | | Prevalence 15% DEFINITION ONE | Prevalence 25% DEFINITION TWO |
| **Sensitivity = 70%** | 0.29 | 0.23 | 0.01 | 0.47 | 48 | 321 | 192 |
| | 0.25 | 0.27 | 0.05 | 0.43 | 66 | 441 | 264 |
| Independence assumption† | 0.156 | 0.364 | 0.144 | 0.336 | 107 | 714 | 428 |
| | 0.05 | 0.47 | 0.25 | 0.23 | 153 | 1021 | 612 |
| | 0.01 | 0.51 | 0.29 | 0.19 | 170 | 1134 | 680 |
| | | | | | | | |

* sensitivity of TRUS = 48% in all cases; ** for 90% power and 2-sided 5% significance; † assumes results of MF-MRI and TRUS are independent for each individual

The shaded regions reflect the scenario in which virtually all cancers are detected by either MP-MRI or TRUS, and so there is extremely low agreement between MP-MRI and TRUS. This does not make clinical sense and is very unlikely but is included for completeness.

# REFERENCES


1. Kirkham AP, Emberton M, Allen C. How good is MRI at detecting and characterising cancer within the prostate? *Eur Urol* 2006;50(6):1163-74; discussion 1175.
2. Chen M, Dang HD, Wang JY, Zhou C, Li SY, Wang WC, et al. Prostate cancer detection: comparison of T2-weighted imaging, diffusion-weighted imaging, proton magnetic resonance spectroscopic imaging, and the three techniques combined. *Acta Radiol* 2008;49(5):602-10.
3. Futterer JJ, Heijmink SW, Scheenen TW, Veltman J, Huisman HJ, Vos P, et al. Prostate cancer localization with dynamic contrast-enhanced MR imaging and proton MR spectroscopic imaging. *Radiology* 2006;241(2):449-58.
4. Kozlowski P, Chang SD, Jones EC, Berean KW, Chen H, Goldenberg SL. Combined diffusion-weighted and dynamic contrast-enhanced MRI for prostate cancer diagnosis--correlation with biopsy and histopathology. *J Magn Reson Imaging* 2006;24(1):108-13.
5. Kumar V, Jagannathan NR, Kumar R, Das SC, Jindal L, Thulkar S, et al. Correlation between metabolite ratios and ADC values of prostate in men with increased PSA level. *Magn Reson Imaging* 2006;24(5):541-8.
6. Macura KJ. Multiparametric magnetic resonance imaging of the prostate: current status in prostate cancer detection, localization, and staging. *Semin Roentgenol* 2008;43(4):303-13.
7. Mazaheri Y, Shukla-Dave A, Hricak H, Fine SW, Zhang J, Inurrigarro G, et al. Prostate cancer: identification with combined diffusion-weighted MR imaging and 3D 1H MR spectroscopic imaging--correlation with pathologic findings. *Radiology* 2008;246(2):480-8.
8. Noworolski SM, Henry RG, Vigneron DB, Kurhanewicz J. Dynamic contrast-enhanced MRI in normal and abnormal prostate tissues as defined by biopsy, MRI, and 3D MRSI. *Magn Reson Med* 2005;53(2):249-55.
9. Reinsberg SA, Payne GS, Riches SF, Ashley S, Brewster JM, Morgan VA, et al. Combined use of diffusion-weighted MRI and 1H MR spectroscopy to increase accuracy in prostate cancer detection. *AJR Am J Roentgenol* 2007;188(1):91-8.
10. Tanimoto A, Nakashima J, Kohno H, Shinmoto H, Kuribayashi S. Prostate cancer screening: the clinical value of diffusion-weighted imaging and dynamic MR imaging in combination with T2-weighted imaging. *J Magn Reson Imaging* 2007;25(1):146-52.
11. van Dorsten FA, van der Graaf M, Engelbrecht MR, van Leenders GJ, Verhofstad A, Rijpkema M, et al. Combined quantitative dynamic contrast-enhanced MR imaging and (1)H MR spectroscopic imaging of human prostate cancer. *J Magn Reson Imaging* 2004;20(2):279-87.
12. Yoshimitsu K, Kiyoshima K, Irie H, Tajima T, Asayama Y, Hirakawa M, et al. Usefulness of apparent diffusion coefficient map in diagnosing prostate carcinoma: correlation with stepwise histopathology. *J Magn Reson Imaging* 2008;27(1):132-9.
13. Harlan SR, Cooperberg MR, Elkin EP, Lubeck DP, Meng MV, Mehta SS, et al. Time trends and characteristics of men choosing watchful waiting for initial treatment of localized prostate cancer: results from CaPSURE. *J Urol* 2003;170(5):1804-7.
14. Ahmed HU, Calleary J, Arya M, Emberton M, Illing RO, Allen C. Re: Dynamic contrast enhanced, pelvic phased array magnetic resonance imaging of localized prostate cancer for predicting tumor volume: correlation with radical prostatectomy findings. A. Villers, P. Puech, D. Mouton, X. Leroy, C. Ballereau and L. Lemaitre, J Urol 2006; 176: 2432-2437. *J Urol* 2007;177(6):2395; author reply 2395-6.
15. Onik G, Miessau M, Bostwick DG. Three-dimensional prostate mapping biopsy has a potentially significant impact on prostate cancer management. *J Clin Oncol* 2009;27(26):4321-6.