
**Multi Parametric Magnetic Resonance Imaging in
the early detection and risk stratification of
prostate cancer: The PROMIS trial**

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I, Ahmed El-Shater Bosaily confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Ahmed El-Shater Bosaily

To my Parents,

The magnitude of your efforts, sacrifices and
uncompromising love and support to each other, my
sister and I remain unfathomable.

There was never a day that you were not there for
us. I Thank god for the blessing that is you every
day

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Abstract: (300)

Although prostate cancer is the most common cancer in men, it remains a difficult and controversial disease in terms of its diagnostic, risk stratification and treatment pathway. This is mainly due to the shortcomings of the standard diagnostic test, trans rectal ultrasound guided biopsy (TRUSBx), that is triggered following an elevated serum prostate specific antigen (PSA) test and the lack of agreement on disease thresholds that correlate to patient risk, if left untreated (and thus undetected). These factors often complicate the selection of the appropriate management that best fits the individual patient.

In this doctoral thesis I propose, examine and validate a different approach that aims to shift the current diagnostic paradigm to that of incorporating an imaging test, multi-parametric magnetic resonance imaging (MP-MRI), prior to TRUS biopsy.

First, I will discuss the nature of prostate cancer and highlight the shortcomings of the current diagnostic pathway and their implications.

Second, I will analyze the shortcomings in early MP-MRI research that might have hindered its acceptance and adoption into the pathway and review the advances in research that occurred since I started my research.

Third, I will discuss the rationale and methodological design considerations behind the PROstate Mri Imaging Study (PROMIS). PROMIS was a multicentre diagnostic paired validating confirmatory cohort study conducted to

provide level 1_b evidence on diagnostic accuracy of MP-MRI. It was designed to avoid the pitfalls identified in the current literature. I will discuss and analyze the design, conduct and results of the trial and its implications.

Finally, I will discuss the wider implications of my work on the clinical practice of prostate cancer management and the future research opportunities made possible by the PROMIS data and its findings.

1. Chapter 1: The current diagnostic pathway

1.1. Prostate cancer: Disease Background (incidence, risk stratification and management

Prostate cancer is the most common male cancer, with a doubling in incidence over the last 15 years in the UK. In 2014, over 46,000 new cases are diagnosed every year in the UK^{1,2} and estimated just over 161,000 new cases in the USA in 2017³.

Yet the majorities of detected cancers are clinically insignificant and have no impact on quality of life or life expectancy. This assertion is supported by significant epidemiological evidence⁴ and most notably several large scale randomized controlled trials of prostate cancer screening. The PLCO (Prostate, Lung, Colon and Ovaries) screening trial in the USA showed no evidence of a survival benefit from an annual prostate cancer screening strategy yet, it was criticised for significant contamination (i.e., Prostate specific antigen [PSA] testing) in the control arm⁵.

The European Randomized Study of Screening for Prostate Cancer (ERSPC) showed a modest reduction in risk of death from prostate cancer in those screened every 4 years, from 8.2% to 4.8% (risk ratio of 0.8 [0.65 to 0.98]) at 9 years' follow-up.⁶ The number needed to screen was 1410 and the number needed to treat was 48 to prevent one death from prostate cancer over a ten-year period⁷. This benefit

was maintained up to 13 years follow-up.⁸ Further, the small survival benefit seemed to be offset by a significant decrease in quality-of-life following post-diagnosis^{9,10}.

The current management of gland-confined prostate cancer is dictated by the perceived risk to the patient as per the 2014 NICE clinical guideline¹¹ described in (table 1.1). Men are classified as having low, intermediate or high-risk disease based on first, their prostate-specific antigen (PSA) serum concentration. PSA is a circulating protein produced by normal prostate tissue. An elevated PSA is a sign that cancer may be present. Second, a histological grading system of the prostatic tissue obtained on biopsy named the Gleason score. A Gleason “pattern” is used to classify prostatic cell differentiation from Gleason 1 (well differentiated, lower risk) to 5 (poorly differentiated, higher risk). The Gleason score is calculated from the sum of the two most common grades of cells. For example, if the man's most common cells are graded as Gleason 3 and Gleason 4, the Gleason score is $3+4=7$.

Third, assessment of the tumor size and extent (T) in accordance with the TNM classification¹² for prostate cancer. The information can be obtained via clinical assessment using digital rectal examination or from diagnostic imaging.

There are several factors that affect the accuracy and utility of this stratification which are discussed in detail in (section 1.2.2)

Risk	PSA, ng/ml	Gleason score	Stage
Low	<10	AND ≤6	AND T1- T2a
Intermediate	10-20	OR 7	OR T2b
High	>20	OR 8-10	OR ≥T2c
<p>Key: T1 - The tumour is too small to be seen on scans or felt during examination of the prostate; T2a – The tumour is in only half of one of the lobes of the prostate gland; T2b – The tumour is in more than half of one of the lobes; T2c – The tumour is in both lobes but is still inside the prostate gland; T3 - The tumour has broken through the capsule of the prostate (locally advanced); T4 - The tumour has spread to other organs nearby.</p>			

Table 1.1: Risk stratification of localised prostate cancer ¹¹

There are many management options available for gland-confined prostate cancer, which can be classified into three large groups: active surveillance, radical prostatectomy and radical radiotherapy. Focal

therapy is an emerging treatment approach that has not yet met with widespread acceptance.

- Active surveillance:

Active surveillance (AS), and its less robust predecessor “watchful waiting” are offered to patients deemed to have low risk prostate cancer. It is also considered in intermediate risk patients with low volume disease. The approach relies on monitoring the disease burden/risk of a patient with a slowly growing disease that may not progress or cause any symptoms. It therefore aims to delay or avoid unnecessary treatments and their detrimental side effects, triggering such treatments if the risk profile increases. Successful active surveillance relies on a strict protocol with the updated version described in (Table 1.2). It must be noted that the use of Multi parametric magnetic resonance imaging (MP-MRI) is a recent addition to the NICE guidelines after the commencement of this research effort. NICE still does not recommend MP-MRI in an initial (triage) diagnostic test prior to biopsy as argued by this work.

However, active surveillance is not without its disadvantages. First, patients on active surveillance have to undergo repeat visits, testing and histological sampling which carries an incremental risk of side effects and also an economical burden. Second, the diagnostic uncertainty associated with the current pathway and the possibility of inappropriate risk stratification carries potential harms to the patient by missing important disease that might progress. Both points are

discussed in detail in (section 1.2.2). Third, patient anxiety with active surveillance limits the quality of life benefits of avoiding radical therapy and plays an important role in triggering radical therapy even if the clinical assessment remains in favour of active surveillance¹³⁻¹⁵.

At enrolment in active surveillance	MP-MRI if not previously performed.	Not applicable.
Year 1	PSA level.	Every 3-4 months ⁽²⁾ .
	PSA kinetics.	Throughout active surveillance ⁽³⁾ .
	Digital rectal examination.	Every 6-12 months ⁽⁴⁾ .
	Prostate re-biopsy.	At 12 months.
Year 2 and beyond	PSA level.	Every 3-6 months ⁽²⁾ .
	PSA kinetics.	Throughout active surveillance ⁽³⁾ .
	Digital rectal examination.	Every 6-12 months ⁽⁴⁾ .

⁽¹⁾ Reassess with MP-MRI if there is concern about clinical or PSA changes at any time during active surveillance; ⁽²⁾ PSA level may be carried out in primary care; ⁽³⁾ May include PSA doubling time and velocity; ⁽⁴⁾ Should be performed by a healthcare professional with expertise and confidence in performing digital rectal examination.

Table 3.2: Active surveillance protocol¹¹.

- Radical prostatectomy and radical radiotherapy

Radical therapy encompasses therapies aimed at the removal/destruction of the whole prostate gland, which includes the varied approaches to radical prostatectomy and external whole gland beam radiotherapy. It is offered to low, intermediate and high risk patients where potential cure or long term disease control is possible in the context of individual patients co-morbidities, life expectancy and expected quality of life after treatment¹¹. Radical therapy despite its therapeutic advantage, comes with significant well documented morbidities including urinary incontinence (5-20%), erectile dysfunction (30-60%) and with radiotherapy, bowel toxicity (5-10%), which impact on the quality of life post treatment¹⁶.

Similar to the findings of large scale screening studies discussed earlier, large scale randomised controlled treatment trials send a very similar message. There is a significant gap between the number of patients diagnosed with prostate cancer and the number of patients who would benefit from treatment.

The Scandinavian Prostate Cancer Group (SPCG-4 trial) randomized clinically diagnosed (non screened) patients which the majority of had clinically significant, medium to high-risk disease between watchful and radical prostatectomy. It showed a survival benefit with long-term

follow-up compared to watchful waiting. Patients younger than 65 years of age showed statistically significant benefits compared to those above 65 independent from the risk stratification of the disease.

On stratification by disease risk, patients with intermediate risk disease gained the maximum benefit from radical management. Low risk patients showed less significant benefit when compared to intermediate risk patients¹⁷. Treatment conferred significant harms and reduction of quality of life to all patients which is to be balanced against survival benefits of treatment in specific risk groups.¹³

The PIVOT (Prostate Intervention versus observation) trial randomized men with early-diagnosed disease via PSA screening between watchful waiting and radical prostatectomy. No cancer-specific survival benefit was identified across the patient population in the study, although subgroup analyses showed that men with high risk disease did survive longer with treatment and there was a possible benefit, albeit marginal, in intermediate risk cancers.¹⁸

The recent publication of the ProtecT (Prostate Testing for Cancer and Treatment) trial¹⁹ results showed that in 1643 men with localized prostate cancer detected on PSA screening, there was no statistically significant difference in prostate-specific or all-cause mortality at 10 years between men randomized to active surveillance, surgery or

radiotherapy, but with higher rates of disease progression and metastases in the active surveillance group.

- Focal therapy

Focal therapy²⁰ of prostate cancer is the concept of treating the areas of the prostate harboring high-risk disease, termed the Index lesion²¹²², while avoiding treating the remaining prostate tissue that might be normal or harbor low risk disease. A variety of ablative techniques including cryotherapy²³, irreversible electroporation²⁴ and high intensity focused ultrasound are used. Focal therapy is a promising concept promising disease control²⁵⁻²⁷ with significantly reduced morbidity compared to radical therapy^{25,28}

Though still recommended only in the research setting¹¹, focal therapy is gaining significant popularity. As it lacks the binary attribute of other therapies, in which the presence or absence of clinically significant disease in the entirety of the gland decides whether a patient gets treatment or not, it requires a more detailed stratification of disease to identify the areas of the gland to target and treat and the accurate assurance of the absence of clinically significant disease in the remaining prostate tissue. Hence selection of the suitable patient requires significantly more information than what is provided by the current diagnostic pathway.

1.2. The current diagnostic pathway

1.2.1. Current practice

At present, a man is deemed at risk of prostate cancer if he has any of the following: a raised serum PSA level, an abnormal digital rectal examination (DRE), a positive family history, or a specific ethnic risk profile¹.

In the context of suspicion of gland confined/early disease, patients positive on PSA or DRE are advised to undergo a trans-rectal Ultrasound (TRUS) guided biopsy. Annually, it is estimated that between 59,000 and 80,000 men have a TRUS biopsy in the UK , about one million in the USA and one million in Europe each year²⁹. However, for the UK, this is likely to be an underestimate considering that 3-4 TRUS-biopsies are usually carried out to diagnose one man with prostate cancer.

If the initial biopsy is negative, patients are followed up using serial PSA readings and in some cases digital rectal examinations. Should there remain a clinical suspicion after the initial negative biopsy (which is a far too common situation in clinical practice) patients undergo repeat TRUS biopsies. In some cases more aggressive biopsy strategies such as saturation trans rectal biopsies or trans-perineal

systematic biopsies are used to confirm or rule out the presence of disease. Recently, the NICE guidelines updated the recommendation regarding patients with negative initial biopsy and now recommends the consideration of MP-MRI (which remains unavailable in the majority of practice settings). If the MP-MRI is negative, no further biopsies are recommended unless the patient exhibits additional risk factors like an abnormal DRE or the presence of atypical small acinar proliferation (ASAP) on the first biopsy among others¹¹. (Figure 1.1) depicts the current standard diagnostic pathway for most patients.

The current diagnostic pathway for gland confined prostate cancer

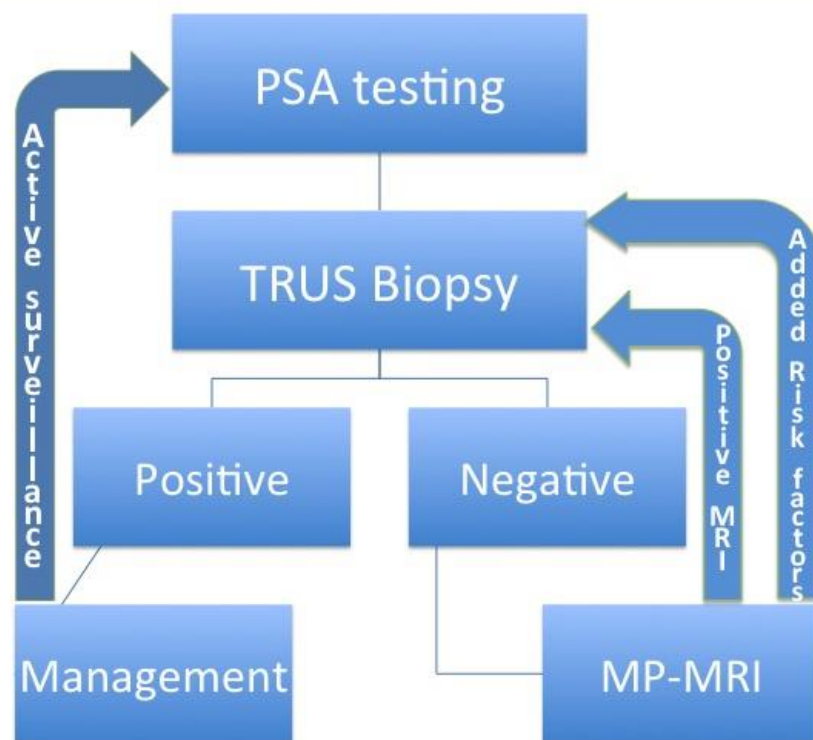


Figure 1.1: The current diagnostic pathway for gland confined prostate cancer

If the initial biopsy is positive, patient risk is stratified as discussed in (section 1.1) and the patient chooses either active surveillance (entailing repeat PSA testing and biopsies) or radical therapy.

1.2.2. Pitfalls of the current pathway

In this section I argue that the current pathway carries significant shortcomings:

- A. It is unable to reliably rule-out the presence of clinically significant prostate cancer (under-detection)
- B. It over-diagnoses clinically insignificant prostate cancer (over-detection)
- C. It is unable to provide sufficient information for accurate risk stratification.
- D. It confers some harms to the patient

This is due to the limitations of individual tests used in the pathway:

1.2.2.1. **The screening test: Serum Prostate specific antigen**

Serum PSA levels are unreliable in the detection of prostate cancer. It is raised due to several benign conditions including benign prostatic hyperplasia and chronic prostatitis. It can be elevated with exercise and sexual intercourse.

As discussed in (section 1.1), several large multicentre trials have demonstrated that PSA has a high false positive rate and triggers unnecessary biopsies that later cause over diagnosis and over treatment of patients with limited benefit to their disease outcomes and quality of life (arguments A and D). This has lead the U.S. Preventive Services Task Force to recommend against PSA screening^{30,31} and recently to only recommend it with informed consent.

1.2.2.2. **The confirmatory test: TRUS Biopsies**

TRUS biopsies are largely conducted in a non-targeted, blind fashion. The ultrasound is used to identify the prostate but cannot identify areas suspicious for gland-confined disease. Hypoechoic lesions on ultrasound have been shown to have a sensitivity of no greater than 50-60% and therefore the evolution of TRUS-biopsy went from targeting these areas or nodules to spreading the

deployment of needles throughout the gland in a 'systematic' fashion.

Although protocols stipulate that the biopsies should sample certain standardized regions in the prostate, studies have shown that does not occur in practice and the biopsies tend to be clustered to certain areas³² with a random deployment pattern. Also, certain areas are usually not sampled resulting in a systematic under sampling error.

These inherent errors lead to a number of problems:

- **Over-diagnosis:** A man who undergoes TRUS biopsy has a 1 in 4 chance of being diagnosed with prostate cancer^{33,34}. This compares with a 6-8% lifetime risk of having prostate cancer that will impact on his life expectancy.

This over-detection of these small low-grade lesions is due in part to the random deployment of TRUS-guided biopsy needles³³⁻³⁵ (Arguments B,C and D) this is demonstrated by (Figure 1.2).



Figure 1.2: Over-detection of clinically insignificant prostate cancer

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

TRUS-biopsies have an estimated false negative rate of 30%-45% although the true false negative rate is unknown as few studies apart from PROMIS have applied a detailed reference test to those men who have a negative TRUS-biopsy.^{36,37}

When clinician obtain representative tissue samples transrectally, (*Figure 1.3a*), several parts of the gland are not well sampled (systematic error). The anterior aspect is missed due to the greater distance from the rectum (*Figure 1.3b,c*). The midline is missed while avoiding the urethra; the apex of the prostate is often difficult to access by the trans rectal route (Arguments A and C)

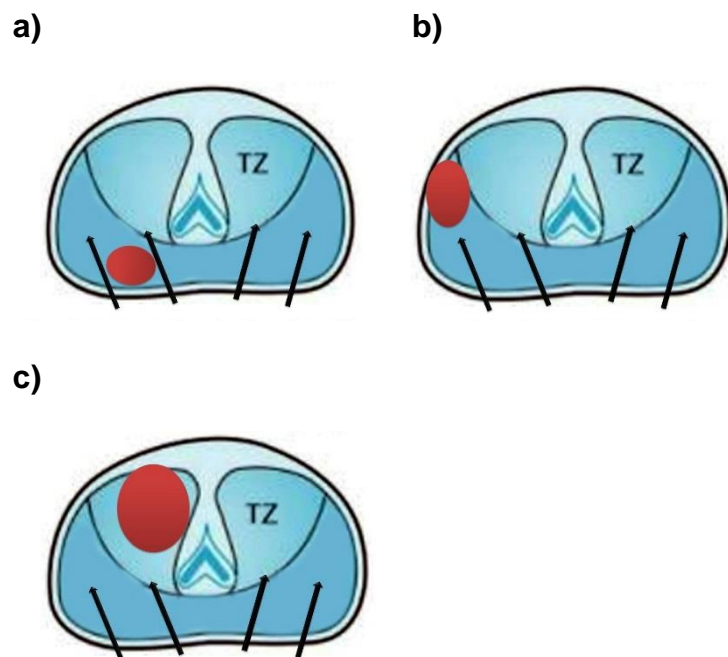


Figure 1.3: Under-detection of clinically significant prostate cancer

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- **Inaccurate risk stratification:** TRUS-biopsies can be unrepresentative of the true burden of cancer due to random sampling error. Either the size or the grade of cancer may be underestimated if the cancer tissue obtained on TRUS-biopsy is not representative.³⁸ (Figure 1.4) 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. (Arguments A and C)

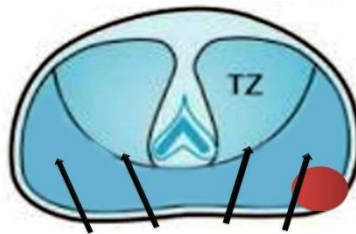


Figure 1.4: *Inaccurate risk stratification*

- **TRUS-guided biopsy has harms.** It 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 expected³⁹⁻⁴².

As the patient progresses in the management pathway, the effects of these errors become evident. The risk of over-staging may result in repeat biopsies with an incremental morbidity in the context of active

surveillance especially as obtaining tissue precisely from the previously sampled area is impossible due to the non targeted nature of TRUS biopsies. It has been shown that in the repeat biopsy settings, TRUS biopsy is not only unreliable in 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.⁴³

Also, unnecessary escalation to radical therapy may happen unnecessarily based on TRUS biopsy results with all the associated morbidities of the treatment that this entails. Similarly poor stratification and false negatives may result in disease progression in patients where early detection was possible.

Finally, the limited information yielded from a TRUS biopsy prevents the patient from benefitting from techniques that aim to dose escalate to tumours (using radiotherapy) and preserve function/reduce positive margins during surgery and recently focal therapy approaches.

2. Chapter 2: MP-MRI imaging in gland confined prostate cancer

2.1. Potential for imaging: The proposed diagnostic pathway

Currently, prostate biopsy is performed in the absence of imaging that can identify a suspicious lesion and direct the biopsy needle to it (section 1.2.2). This approach contrasts markedly with that used for most solid tumors, in which the physician either visualizes (e.g. at endoscopy) or images (e.g. using mammography) a suspect lesion in order to guide a biopsy needle to it.

In this work I propose a different diagnostic approach dependent on the use of MP-MRI carried out after an elevated PSA but before a TRUS-biopsy, in a manner to that of a triage test⁴⁴. Patients suspected to have prostate cancer would have an a MP-MRI prior to their biopsy in order to help decide if the patient should or should not have a prostate biopsy, and if positive, guide biopsies to target suspicious lesions as depicted in (*Figure 2.1*).

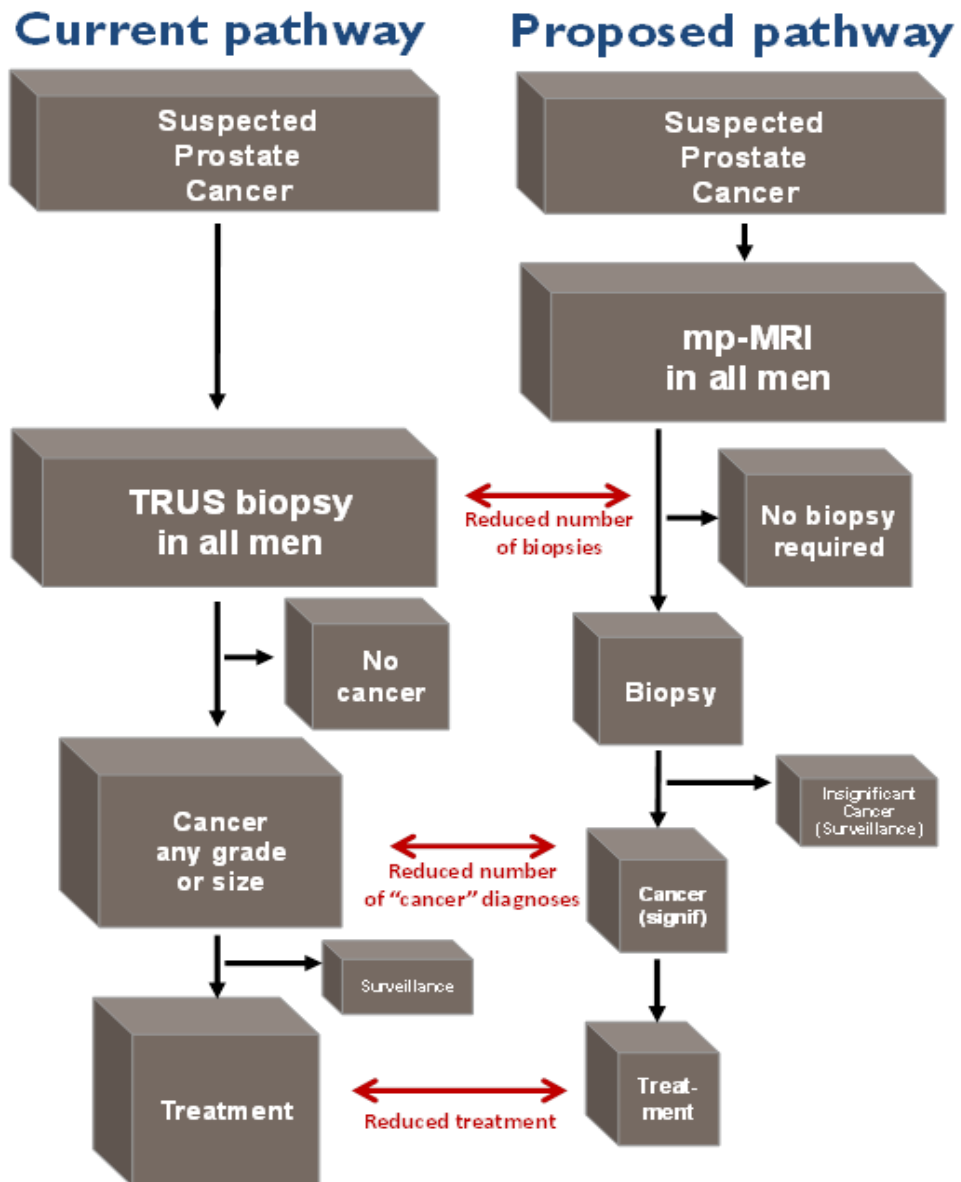


Figure 2.1: Current and proposed diagnostic pathway for prostate cancer.

The use of MP-MRI prior to TRUS-biopsy 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.
 - **Improved appropriate treatment selection** due to the improved risk stratification. Also, imaging might allow better surgical planning and also inform tissue-preserving strategies such as active surveillance or focal therapy.
 - **Reduced complications (sepsis and bleeding)** as fewer men biopsied and fewer biopsies taken in men that are biopsied.

In addition, a revised diagnostic pathway based on the findings of PROMIS also has the *potential* to offer a more cost-effective use of NHS resources.

2.2. Early MP-MRI literature: findings and limitations

Prior to the commencement of recruitment to the PROMIS trial in 2012, the state-of-the-art evidence at the time suggested MRI had the desired attributes of a test that could be used in the prostate cancer diagnostic pathway. Kurhanewicz et al's review suggested a sensitivity and specificity ranging between 70-90% in identifying clinically relevant

prostate cancer⁴⁵. Yet MRI was not adopted into the pathway and was not accepted by mainstream clinical practice. This was due to several reasons. The most pertinent, following a systematic review of the literature⁴⁶, was that the quality of the initial studies evaluating MRI were disappointing⁴⁷. They repeatedly showed low sensitivity and specificity as well as high inter-observer variability, even when using high-resolution endorectal coils⁴⁸⁻⁵⁴.

Since those initial reports, there were several important improvements to the conduct and practice of MP-MRI research. Appreciation of the impact of post-biopsy changes on MRI which caused artefactual changes making interpretation difficult led to propositions to delay post biopsy imaging. Technological improvements such as stronger and improved MRI scanners (from 0.5 Tesla to 1.5 Tesla and 3.0 Tesla), technical improvements such as the use of pelvic phased arrays (if not endorectal coils), development of shorter pulse sequences allowing faster image acquisition, and the adoption and improvement of diffusion weighting (DW) and dynamic contrast-enhancement (DCE) sequences.

Most notably, and probably the greatest impact, was in recognition of the value of combining multiple MRI sequences (T2 weighting (T2), diffusion weighting (DW) and dynamic contrast enhancement (DCE) sequences) and the adoption of a true multi-parametric approach (MP-MRI, combining these three sequences together)⁵⁵⁻⁶⁶. Despite the

small sample size, single centre case series found an advantage in using two or three MR sequences rather than just one.

However, even with these improvements in technological aspects of the imaging, the literature prior to PROMIS had several key limitations⁶⁷ that contributed (among other limitations discussed in details in (sections 2.2 & 2.3) to the lack acceptance of MP-MRI in the diagnostic pathways⁶⁸ :

- **Biopsy artefact:** studies mostly evaluate MRI after biopsy. However, the haemorrhage and biopsy related changes could affect what is seen on the MRI resulting in increase in false positive or negative rates.
- **Limited application:** studies mostly evaluate only the peripheral zone of the prostate, ignoring the transition/central zones where up to one third of prostate cancers which are also difficult location to assess with the limitations of TRUS biopsy (section 1.2.2.2)
- **Segmentation:** due to the small sample sizes, the prostate was segmented into regions of interest (ROI) with each segment treated independently as positive or negative to generate a sample size, increasing the power and accuracy of the analysis, which is not methodologically sound.

-
- **Poor reference standard:** As discussed in (section 1.2.2.2), The limitations of TRUS-biopsy makes the procedure a poor diagnostic standard and not suitable as a reference standard in the context of a research study aiming to validate MRI. Studies used radical prostatectomy, leading to selection bias as those undergoing surgery definitely have burdens of cancer that are distinct from men with an abnormal PSA, and patients with no cancer or choosing other treatments can never be evaluated with extirpative surgical specimens.⁶⁹ Further, co-registration of an image to an whole-mount specimen is challenging because of shrinkage (10-20%), distortion, tissue loss as a result of 'trimming' (10%), orientation, and absent perfusion.
 - **Lack of imaging protocol recommendations:** As there was no agreed guideline on the conduct of MP-MRI, most papers used different combination of sequences with variable imaging parameters contributing to the variation in results on systematic review.

2.3. Updates to the MP-MRI literature

Since the design phase and then start of recruitment to PROMIS, I recognise that there have been notable additions to the body of literature on MP-MRI. Twelve reports⁷⁰⁻⁸¹, two systemic reviews^{67,82},

followed by an update⁸³, have been published. There has been significant improvement in the methodology and conduct of research work. More accurate reference standards were employed and more uniform imaging parameters were used as a result of consensus statements standardising the conduct and reporting of MP-MRI. Despite these improvements and favourable diagnostic accuracy measures in the majority of these papers, there was still significant variation in the accuracy measures of prostate MP-MRI across authors, which was evident on systematic review of the literature⁸². Where the reported diagnostic accuracy measures showed a significant range. A sensitivity range of 58–96%, specificity 23–87%, positive predictive value 34–93% and negative predictive value 63–98%. These variations are caused by specific methodological challenges, which are discussed in detail in (section 2.4). Before MP-MRI is to be adopted on a large scale, higher levels of evidence and knowledge of diagnostic accuracy are still needed.

Prior to PROMIS, none of the available literature was able to produce level 1 evidence on its accuracy and none of the studies prospectively evaluated the clinical validity of MP-MRI in the population of interest against an accurate and appropriate reference standard within a multi-centre setting in a double-blinded fashion.

2.4. Methodological considerations in diagnostic validation of MP-MRI

As discussed in (section 2.2) and (section 2.3), there were significant shortcomings in the level of evidence available on MP-MRI and concerns were raised regarding the methodological quality and risks of bias in a significant majority^{67,82}. On reflecting on the evidence several key shortcomings become apparent. This has been covered extensively in published clinical and systematic reviews. Below, I discuss the most relevant to the assessment of MP-MRI in context of a triage test in a new diagnostic pathway:

- **Introduction of biases⁸⁴:**
 - **Selection / spectrum biases**, which occur when the tested sample (patients) is not representative of the disease in the general population. They are normally introduced when studies limit their patients to, for example, patients who have previously had a negative biopsy^{71,74,76,78,81}, raising the possibility of a high prevalence of difficult-to-diagnose disease (which may reside in one or two areas of the prostate, anteriorly or apically, for instance). Similarly, the use of radical prostatectomy⁷³ as a reference standard limits the population to higher risk, higher burden disease, falsely improving the diagnostic performance of the test.

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- **Diagnostic review bias**, which occurs when the index and reference tests are not blinded and are not reported independently from each other. There is limited information in publications on whether and how blinding was maintained and in several^{74,76-78,80,81}, blinding was abandoned in favor of targeted histological samples.
 - **Incorporation bias** is introduced in this setting, when the index test results dictate whether and how the reference test is undertaken. As in studies in which only trigger biopsies based on a positive MP-MRI lesion, as the adopted strategy by most^{70-72,74,76,80,81} studies. This is particularly detrimental in assessment of negative predictive values, as it assumes that all negative cases for the index test are true negatives hence the reliability of these findings in a triage setting is limited.
 - **Sample size selection:** An appropriate sample size selection is important to ensure that the various stages and variations of the assessed condition in the general population are well represented in the sample and reflected in the results. Detailed description of sample size calculations are discussed in (*section 3.9.7*) below. Unfortunately, none of the publications reported power calculations or a clear methodological rationale behind their sample size even when prompted⁸⁵.

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- **Variability assessment:** The current literature did not assess the performance of MRI in different practice settings. All the studies were conducted in expert sites. All were in a single centre except one⁸³ which was conducted in two expert centres, and inter-observer agreement was reported by only one study⁸³ which was confined to expert radiologists only.

All studies conducted their scans on the same scanner from the same manufacturer, leaving no opportunity to assess if the use of different scanners and different manufacturers had an impact on the performance characteristics of the index test. This again is not reflective of a widely applied diagnostic pathway across smaller district hospitals (as to be expected for a triage test) with variable experience and training of radiologists, different types and versions of scanners and the difference MRI manufacturers.

Definition of significant disease: Unfortunately, there is no widely accepted definition of clinically significant prostate cancer on histological sampling. The inaccuracies of TRUS biopsy cause a significant variation in results between biopsy and radical prostatectomy (RP). The diagnosis can change from positive to negative in up to two-thirds of men on active surveillance⁸⁶. At least one third of men are incorrectly classified by Gleason grade at diagnosis and up to 50% are misclassified by disease burden

(volume)^{37,87}. Also, the previously adopted criteria such as Epstein or Stamey⁸⁸⁻⁹¹, were dependant on TRUS-driven sampling. These criteria are not suitable to apply to more accurate biopsy approaches, which in detecting more disease than a standard TRUS inflate patients' risk if the same criteria are applied – this is especially true if the number or percentage of cores is used to risk stratify.

Recently, approaches based on more accurate histological reference standards⁹², and further research into the risk of progression and metastasis⁹³ have provided much needed clarity although consensus has still not been achieved^{94,95}.

3. **Chapter 3: The *PROMIS* trial rationale and methods:**

3.1. **Introduction**

PROMIS was designed to provide definitive level 1_b⁹⁶ evidence (as defined by the Oxford Centre for Evidence Based Medicine) on the diagnostic performance of MP-MRI in diagnosis of early prostate cancer. PROMIS was conducted in response to the literature shortcomings discussed earlier and the significant clinical and health economics need of a better diagnostic strategy for prostate cancer.

3.2. **Trial registration**

PROMIS was registered on clinical trials.gov (NCT01292291) and controlled-trials.com (ISRCTN 16082556).

3.3. **Funding**

PROMIS received funding and support from the following:

UK Government Department of Health, National Institute of Health Research – Health Technology Assessment Programme (Project number 09/22/67). *Department of Health Disclaimer:* The views and opinions expressed herein are those of the authors and do not necessarily reflect those of the health technology assessment program, NIHR, NHS or the Department of Health.

Also supported and partially funded by UCLH/UCL Biomedical Research Centre and The Royal Marsden and Institute for Cancer Research Biomedical Research Centre. PROMIS was coordinated by

the Medical Research Council Clinical Trials Unit (MRC CTU) at UCL and sponsored by University College London (UCL).

3.4. Ethical considerations

The study was carried out in accordance with the principles of the Declaration of Helsinki and the UK Research Governance Framework version 2, and received UK Research Ethics Committee approval on 16th March 2011 by the NRES Committee London-Hampstead. PROMIS was registered on clinical trials.gov (NCT01292291).

3.5. Trial management

PROMIS was overseen and managed by a Trial Management Group (TMG), representing the participating sites and academic centres. It oversaw the conduct of the trial across centers on monthly basis. Also, a patient and public advocate was a member of TMG and consulted on trial management decisions.

PROMIS and the TMG were in turn overseen by an independent Trial Steering Committee (TSC), which also functioned as the Independent Data Monitoring Committee (DMC). The TSC received regular updates on the progress and monitored the data (as DMC) independently. The TSC also conducted weekly reviews of the rate of adverse effects and conducted reviews of PROMIS at specific time-points as detailed further in the following sections.

PROMIS was set up to run in two stages: a pilot phase, followed by a main phase. The pilot study recruited 50 patients over one year to allow testing of safety and recruitment. The pilot phase was completed in May 2013 and independently reviewed by the TSC who recommended continuation of the study into the main phase without any changes to the design.

Details on the members of the PROMIS group, the TMG and the TSC are attached in (*Appendix I*).

3.6. Objectives and outcomes:

The purpose of PROMIS was to assess the clinical validity (sensitivity, specificity, positive and negative value) of multi-parametric Magnetic Resonance Imaging (MP-MRI) for the detection of clinically significant prostate cancer in biopsy naïve men and compare these metrics to those of TRUS-biopsy.

Specifically, PROMIS evaluates whether MP-MRI improves the ability to rule-in as well as rule-out clinically significant prostate cancer in a group of men at risk of prostate cancer, who have not had previous biopsies and are at the point in standard care where they would be advised to have prostate biopsy.

PROMIS was designed to determine whether it is appropriate that men with a risk factor for harbouring clinically significant cancer should

initially receive a MP-MRI to select those who need a prostate biopsy and those who could safely avoid a first prostate biopsy. In other words, we sought to determine whether MP-MRI could be used as a triage test prior to first biopsy⁴⁴(**Figure 2.1**)

The main objectives of the trial were:

- **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, by assessing the accuracy of both MP-MRI (the index test) and TRUS-biopsy (standard test) against an accurate gold reference standard, template prostate mapping (TPM) biopsy.**
- **To estimate the cost-effectiveness of an MP-MRI based pathway. Using data from PROMIS and the wider literature, the study will consider the implications of alternative diagnostic strategies for NHS cost and men's quality-adjusted survival duration.**

The primary and secondary outcomes of PROMIS are detailed in (*Table 3.1*).

Primary outcomes:
Proportion of men who could safely avoid a biopsy as determined by specificity and negative predictive values (NPV), based on definition ONE of clinical significance as assessed by TPM.
Proportion of men correctly identified by MP-MRI to have clinically significant prostate cancer as determined by sensitivity and positive predictive value, based on definition ONE of clinical significance as assessed by TPM.
Secondary outcomes:
The proportion of men who could safely avoid biopsy, given that they do not have DEFINITION TWO 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.

Table 3.1: Primary and secondary outcomes of the PROMIS trial.

3.7. Trial design

PROMIS was a prospective, STARD (standards of reporting diagnostic accuracy statement) compliant⁹⁷, validating paired cohort confirmatory study⁴⁴ geared to provide level 1b evidence for diagnostic studies⁹⁶.

The population of interest was men at risk of prostate cancer who are usually recommended to undergo a first prostate biopsy within standard care.

PROMIS was conducted at 11 NHS hospitals in England. To compare the diagnostic accuracy of MP-MRI (the index test) and TRUS biopsy (the current standard), both were individually compared to a reference standard, 5mm trans-perineal mapping ultrasound guided biopsies (TPM). Therefore, all PROMIS patients underwent all three tests (MP-MRI, TPM biopsy and TRUS biopsy), with TPM biopsy followed by TRUS biopsy performed as a combined prostate biopsy (CPB) procedure. The trial schema is depicted in (*Figure 3.1*). Each test was conducted blind to all the other test results and reported independently of the other tests. There are several methodological advantages in adopting such design, which I discuss in (section 7.1)

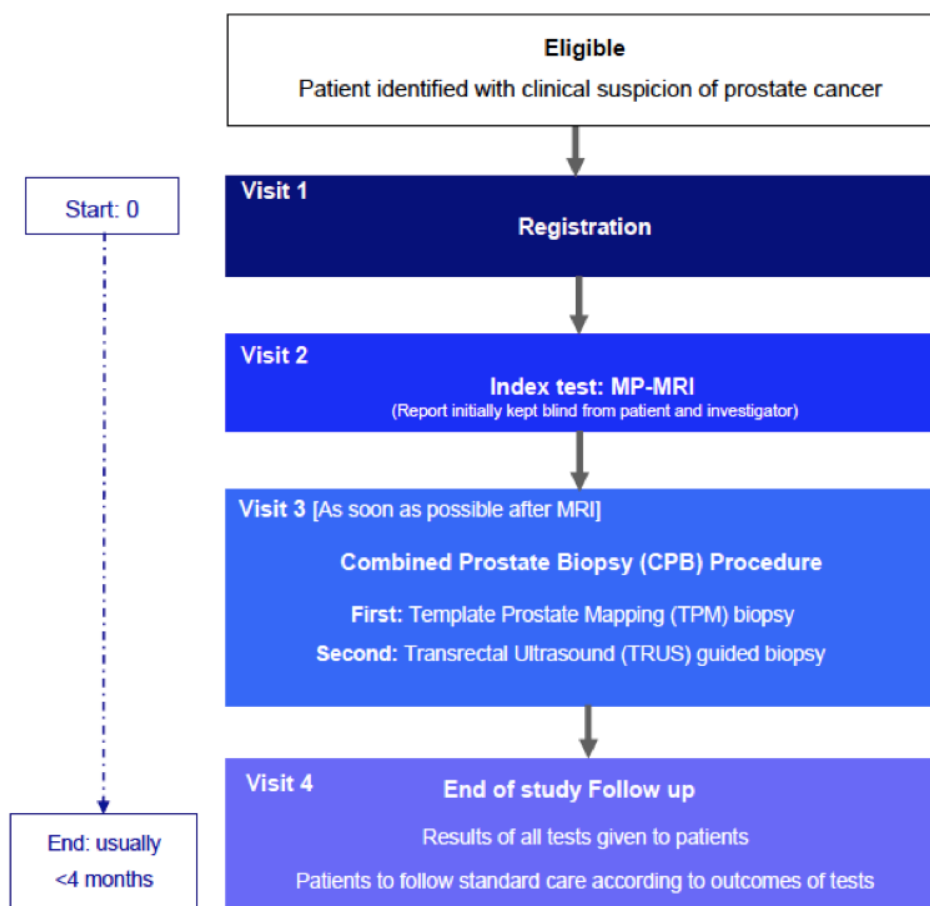


Figure 3.1: PROMIS trial schema

3.8. Eligibility criteria

Patients were eligible to enroll into the study if they fulfilled all the inclusion criteria and none of the exclusion criteria detailed in (Table 3.2). All men were required to provide written informed consent prior to enrolment. Patients willing to contribute additional serum and urine samples to the translational arm of the study (PROMIS-T) consented to do so in addition to the standard PROMIS consent. The standardized consent proforma can be found in (Appendix II).

Inclusion criteria
Men at least 18 years or over at risk of prostate cancer who have been advised to have a prostate biopsy
Serum PSA \leq 15ng/ml within previous 3 months
Suspected stage \leq T2 on rectal examination (organ confined)
Fit for general/spinal anaesthesia
Fit to undergo all protocol procedures including a trans rectal ultrasound
Signed informed consent
Exclusion criteria
Treated using 5-alpha-reductase inhibitors at time of registration or during the prior 6 months
Previous history of prostate biopsy, prostate surgery or treatment for prostate cancer (interventions for benign prostatic hyperplasia/bladder outflow obstruction is acceptable)
Evidence of a urinary tract infection or history of acute prostatitis within the last 3 months
Contraindication to MRI (e.g. claustrophobia, pacemaker, estimated GFR \leq 50)
Any other medical condition precluding procedures described in the protocol
Contraindications for MRI (history of hip replacement surgery, metallic hip replacement or extensive pelvic orthopaedic metal work).

Table 3.2: Inclusion and exclusion criteria in PROMIS.

We excluded men with PSA >15ng/ml as first, they are likely to have a high incidence of locally advanced or metastatic cancer, which is not the intended assessment group for a future and potential triage test. Advanced disease means they are not likely to receive or need a MP-MRI as a triage scan, as they would proceed to biopsy regardless of the MP-MRI findings.

Second, with the possibility of a large burden or advanced disease, these patients would benefit more from prompt, swift management under standard care pathways rather than receiving a detailed risk stratification via PROMIS and there may be potential harms if their management was delayed in favor of conducting a research trial.

Also, we withdrew men whose prostate volume was found at MP-MRI to exceed 100cc from the study as these patients had an increased rate of complications post CPB and the 5mm sampling process was likely to be incomplete and inaccurate due to the gland's initial size and biopsy associated swelling and oedema during the conduct of CPB causing it to swell further as well as the lack of being able to sample the lateral and anterior parts of the prostate due to the pelvic arch.

3.9. Trial interventions

3.9.1. *The index test: multi-parametric magnetic resonance imaging (MP-MRI)*

MP-MRI was standardized to the minimal requirements advised by a European consensus meeting⁹⁸, the European Society of Uro-Radiology⁹⁹ and the British Society of Uro-Radiology guidelines¹⁰⁰. T1-weighted, T2-weighted, diffusion-weighted (apparent diffusion coefficient maps and long-b scan) and dynamic gadolinium contrast-enhanced imaging was acquired using a 1.5 Tesla scanner and a pelvic phased array. Scanning parameters are detailed in (*Table 3.3*)

	TR	TE	Flip angle/ degree	Plane	Slice thickne ss/Gap	Matrix Size	Field of View/m m	Time from scan
T2 TSE	5170	92	180	Axial, coron al, sagitt al	3mm (10% gap)	256x2 56	180x1 80	3m 54s (ax)
VIBE at multiple flip angles for T1calculat ion(option al)								
VIBE fat sat	5.61	2.52	15	Axial	3mm	192x1 92	260x2 60	Continue for at least 5m30s after contrast
Diffusion (b values: 0, 150, 500, 1000)	2200	Min (<98)		Axial	5mm	172x1 72	260x2 60	5m 44s (16 average)
Diffusion (b=1400)	2200	Min (<98)		Axial	5mm	172x1 72	320x3 20	3m 39s (32 averages)

Table 3.3: MP-MRI scan specification

Endorectal coils were not included as there was no consensus on their role in minimal scanning requirements.⁹⁸ Magnetic resonance spectroscopy was not included as evidence from a large multicentre study at the time showed no added benefit in detection in comparison to T2-weighted imaging alone¹⁰¹. Also, spectroscopy is a highly specialized test and is not feasible to conduct in a large-scale triage capacity. We made the conscious decision to only include 1.5T scanners since they are the most widely available in the UK NHS (national health service) setting and most studies in the literature had reported accuracy of MP-MRI based on 1.5T scanners alone. Indeed, if 1.5T was accurate, it was safe to assume that 3T was at least equally accurate; making the contrary assumption would not be accepted.

Quality assurance

A robust quality assurance and quality control process was used to ensure the standardization and maintain the quality of each scan and ensure uniformity across all centers. All MRI scanners and imaging protocol setup was reviewed, verified and signed at participation in PROMIS. Also each individual MP-MRI scan underwent quality control checks. This was undertaken by an

independent commercial imaging clinical research organization appointed through open tender (Ixico Ltd, London, UK).

Prior to site initiation, the lead radiologist (Kirkham) reviewed a number of prostate MRIs from each center and gave iterative feedback on improving scan quality until the desired level of quality was achieved before the site was allowed to recruit.

During the study, scans deemed of insufficient quality were repeated prior to biopsy. Scans were also repeated if biopsies were delayed by more than 3 month for any reason.

Also, all radiologists participating in the study received training covering the trial rationale, conduct and standard operating procedures. They also received detailed training on reporting the scans by the lead radiologist (Kirkham).

Standardized reporting:

A standardised operating procedure for MP-MRI reporting (*Appendix II*) was adopted in line with the recommendations of the European consensus meeting and the European Society of Uro-Radiology prostate MRI guidelines.⁹⁹ This was convened before publication of the more recent Prostate Imaging and Data Reporting System (PIRADS) MP-MRI reporting consensus.

Subsequent comparisons of the Likert and PIRADS reporting schemes have yielded similar results.^{102,103}

At each centre, MP-MRI scans were reported by dedicated urologic radiologists who have undergone centralized training provided by the lead center (UCH). Radiologists were provided with clinical details including PSA, DRE findings and any other risk factors such as family history. This reflects how imaging is reported in standard clinical practice.

Images were reported in sequence, with T2-weighted images reported first, T2-weighted and diffusion-weighted images reported together, and then a third report issued for T2-weighted with diffusion and dynamic contrast enhanced (DCE) scans together. The reporting form is shown in (*Figure 3.2*). This is to allow further analysis and investigate the added diagnostic value of each sequence as discussed in *section (11.1)*

A 1 to 5 Likert scoring system^{98,99,104} was used to indicate the probability of cancer (1, highly likely to be benign; 2, likely to be benign; 3, equivocal; 4, likely to be malignant; 5, highly likely to be malignant). The prostate was divided into 12 regions of interest and each region scored from 1 to 5. Also, each lesion was identified and scored separately, and the longest axial diameter, lesion volume, apparent diffusion coefficient (ADC) value and contrast

enhancement curve type were recorded¹⁰⁵⁻¹⁰⁸. From these observations, an overall score of 1 to 5 as above was assigned to the whole prostate. This was carried out for 'any cancer' and for definitions 1 and 2 of clinically significant cancer (section 3.9.5).

The overall score was used for the primary outcome and an overall score of 3 or more was used to indicate a suspicious scan for clinically significant cancer (i.e., a positive MP-MRI). This reflects the threshold to which further tests (e.g. biopsy) would be considered if MP-MRI were to be introduced into the diagnostic pathway in the future.

Inter-observer agreement:

To assess inter-observer agreement initially, 132 scans from the lead site were re-reported by a blinded second urologic radiologist based at that site. The second radiologist was given the same clinical information.

Blinding:

Radiologists were blinded to the conduct and results of all other aspects of the trial. Similarly, all other clinicians involved were blinded to the MP-MRI. Due to the following reasons, radiologists

were asked to unblind the patient's MRI to the remaining clinicians if:

- The scan revealed an enlarged prostate volume >100ml, which would be impossible to sample every 5mm due to the interference of the bony pelvic arch. This might have reduced the number of 'negative' prostates in the final analyses as BPH – the cause of very large prostates – gives rise to false positives in elevated PSA levels.
- The scan revealed evidence of T4 prostate cancer or involved lymph nodes or colorectal/bladder invasion. This might have had a detrimental impact on the performance characteristic of MP-MRI as such tumours were more likely to be MRI-detected but would not contribute to diagnostic sensitivity analyses. The presence of other cancers such as bladder or colorectal cancers was also a criterion for unblinding and withdrawal. Withdrawal was deemed appropriate in these men also for patient safety concerns as expedited referral for biopsy and treatment was required. These latter withdrawals were unlikely to impact on the primary or secondary outcomes.

Patient's Initials: Date of Birth: Trial No.: Reporter: ☐ Local ☐ Central ☐ Additional ☐
Hospital Number: Scan Date: Are you blind to all results for this patient? Yes ☐ No ☐
PSA ng/ml: Tesla scanner: 1.5 ☐ OR 3.0 ☐

1. SIZE OF PROSTATE

Transverse cm Anterior-Posterior cm Cranio-Caudal cm Volume cm³
If gland volume is $\geq 100\text{cm}^3$ submit this form immediately to the MRCCTU and complete a withdrawal form.

2. SECTOR (for UCL Definition Two disease) (Report strictly in order, and put a value 1-5[†] in each ROI). P = Posterior <1.7cm (measured from posterior capsule)

	T2	T2 + DW	T2 + DW + DCE
Base A			
Base P			
Mid A			
Mid P			
Apex A			
Apex P			

Risk category	Disease Threshold	MRI Score [†] (1-5)		
		R	L	Overall
Any cancer	Any Disease			
Definition Two (Primary outcome)	$\geq 0.2\text{cc}$ and/or $\geq 3+4$			
Definition One	$\geq 0.5\text{cc}$ and/or $\geq 4+3$			
Dominant Gleason 4	$\geq 4+3$			

3b. INDIVIDUAL LESIONS

(Using the lesions drawn in 3a please score each lesion on the table below)

Lesion No.	T2	D	C	All	Curve 1=Slow rise 2=Flat 3=Early peak	ADC	Zone	Max diameter	Volume (cm ³) or Diffuse	Distance from posterior capsule	Estimated Gleason Grade	Estimated Cancer Significance
	MRI Score [†] (For T2, D, C: 1-5 as on ESUR 2012 guidelines)				1-3	Value	PZ/TZ/CZ/Combination	mm		mm	e.g. 3+4	Not sign/Def2/Def1
1											+	
2											+	
3											+	
4											+	
5											+	
6											+	

4. STAGING

	Vesicles involved?	Extra-capsular?	Sphincter (T4)?	Rectum (T4)?	Nodes?
MRI Score [†] (1-5)					
If score >2, Left or Right?					

If score for nodes >2, max short axis nodal diameter? (mm)

† MRI Score

1=Highly likely benign
2=Likely benign
3=Equivocal
4=Likely malignant
5=Highly likely malignant

Signature: Author Name: Report Date:

Please email a scanned copy to MRCCTU.PROMIS@ucl.ac.uk

Figure 3.2: MP-MRI reporting form

3.9.2. The standard test: trans rectal ultrasound-guided (TRUS)

biopsy

TRUS-biopsy of the prostate was performed after TPM-biopsy in the same session under the same general/spinal anaesthetic as a combined prostate biopsy procedure. The reasoning behind this approach was guided with both methodological and patient related factors.

First, to ensure that results for the reference test (i.e. TPM-biopsy) were obtained in an optimal fashion in a biopsy-naïve gland that had not undergone swelling and deformation (that might have resulted from TRUS-biopsy needling). Second, It theoretically minimizes the risk of infection, as the potential for faecal contamination was restricted to the end of the procedure. Third, it reduces the burden of visits and the discomfort of experiencing two separate biopsy visits to participating patients. Last, combining the two on one day minimises dropout of patients between tests.

The clinician performing the biopsy procedure was blind to the MP-MRI results so that suspicious areas would not be targeted during the TRUS-biopsy and the fidelity of the TPM-biopsy reference test was maintained. TRUS-biopsies were taken as per international guidelines¹⁰⁹ and incorporated 10-12 core biopsies. Each core was identified and potted separately. The TPM-biopsies and TRUS-

biopsy sets from individual patients were sent to different pathologists to minimize review and work-up biases. (*Appendix 2*) contains the detailed standard operating procedures for the conduct of TRUS biopsy.

3.9.3. The reference standard: trans-perineal template prostate mapping biopsy (TPM)

Trans-perineal Template Prostate Mapping (TPM) biopsies depicted in (*Figure 3.3*) is conducted first followed by TRUS-biopsies under general/ spinal anaesthesia as a combined prostate biopsy procedure (CPB) in the same session.

Using trans rectal ultrasound imaging, the prostate is sampled through the perineum using a 5mm spaced grid for needle guidance. Each prostate is sampled in 5mm intervals along the X and Y coordinates on the sampling grid once from the apex (caudal half of the gland) and a second sample from the base (cranial half of the gland) with exclusion of the 5mm interval corresponding to the anterior urethral zone to avoid injuring the urethra (*Figure 3.3*). The standard operating procedures for the conduct of TPM-biopsies are attached in (*Appendix II*).

TPM-biopsy produces a histological map of the entire prostate in 3-dimensions with an estimated sensitivity and negative predictive

value (NPV) in the order of 95% for clinically significant cancers when assessed against radical prostatectomy^{110,111}. TPM-biopsy meets the required specification as a gold standard reference test for our defined population^{110,112-116}. TPM also is applicable to most men with suspicion of prostate cancer so unlike RP, selection and spectrum bias would not be introduced. This is discussed further in (chapters 2 & 7).

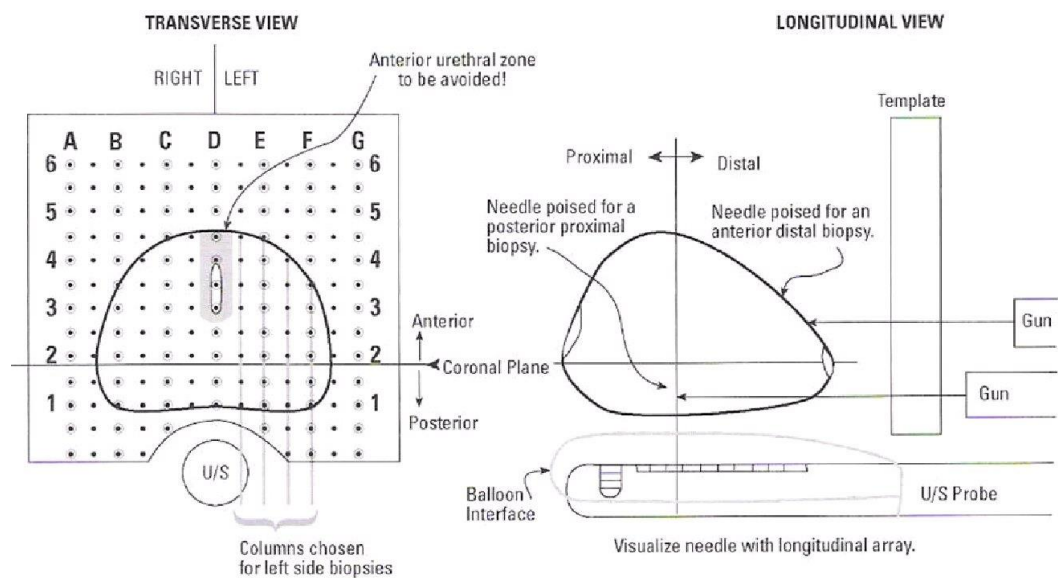


Figure 3.3: Illustration of how Trans-perineal Template Prostate Mapping biopsies are conducted

Centres were selected for their prior experience in carrying out TPM-biopsies, and training was provided to all centres in the conduct of TPM according to the PROMIS protocol.

The side-effect profile of TPM-biopsy is comparable to that of TRUS-biopsy, with exceptions being that retention is higher and sepsis is lower compared to TRUS-biopsy. A combined procedure

under general/spinal anaesthesia was never attempted before in a trial setting although a retrospective study raised no safety issues¹¹⁷. (*Table 3.4*) details the expected and estimated side effect profile of CPB in comparison to TRUS-biopsy which was used as part of the patient information sheet and reviewed with the PROMIS clinician before consent (*Appendix I*).

<div> <div>Procedure</div> <div>Side effect</div> </div>	TRUS alone (standard care)	Combined biopsy: TPM +TRUS (in the PROMIS study)
Pain/Discomfort	Almost all men experience temporary discomfort in the rectum	Almost all men experience temporary discomfort in the rectum
Burning when passing urine	Almost all men	Almost all men
Bloody Urine	1 in 2 men (self-resolving, 2-3 days)	Almost all men (self-resolving, 2-3 days)
Bloody Sperm	3 in 10 men (2-3 months to resolve)	Almost all men (lasting up to 3 months)
Poor erections	3 in 10 men (self-resolving after 6-8 weeks). Rarely, tablets may be needed to help the erections	Almost all men (self-resolving after 6-8 weeks). Rarely, tablets may be needed to help the erections

	improve.	improve.
Infection of skin or urine	1-8 in 100 men	1-8 in 100 men
Infection of skin or urine requiring admission and intravenous antibiotics	Between 1-4 in 100 men	Between 1-4 in 100 men
Difficulty passing urine*	1 in 100 men	1-3 in 20 men*.
Bruising of skin	None	Almost all men
Bruising spread to scrotum	None	Between 1 in 20 to 1 in 10 men

** We noted the high rate of retention with the combined biopsies within our pilot phase of the trial. We responded to that by keeping a temporary urinary catheter (which is fitted during the procedure to delineate the urethra prior to biopsy) for a period of 5-7 days after the procedure which we then removed and performed a urine analysis to pre-empt any potential infection. This practice has resolved the problem of retention while the gland swelling subsides and patients find it tolerable.*

Table 3.4: combined prostate biopsy procedure side effect profile as stated in the patient information sheet and consent documentation.

3.9.3.1. **Changes in the conduct of CPB in the main phase**

After the pilot phase, several lessons were learned from the initial experience with the PROMIS patient pathway and some amendments were made in response:

TRUS biopsies were conducted in the left lateral position to simulate the conduct of TRUS-biopsy in normal clinical practice. After feedback from our anesthesiology colleagues, moving the patient from the supine lithotomy position in which the TPM-biopsies were conducted, to a left lateral position while under anesthesia was impractical. Repositioning was time consuming and laborious, which resulted in an unnecessary increase in operative time for the patient increasing the risk of post procedure urinary retention and the risks of anesthesia. It may also cause technical difficulties with maintaining the patient's airway in this position, which may necessitate unnecessary intubation due to the laryngeal mask slipping out of position.

In response we conducted the TRUS-biopsies in the supine position after TPM-biopsy without moving the patient during the main phase. This was done after a discussion within the TMG, which also included advice from independent urologists with respect to how this change may impact the accuracy assessment of TRUS-biopsies as a reflection to daily clinic practice. It was

agreed and later reviewed and approved by the TSC that the change will have no negative impact on the assessment of TRUS-biopsy accuracy, other than from a theoretical improvement of accuracy due to the relatively easier access with TRUS-biopsies in a supine position under anesthesia, which eliminates patient discomfort (*Appendix II*).

Template mapping biopsies were conducted in the same manner operatively across all phases of the trial. In the pilot phase, each core obtained during the procedure was stained immediately with the cranial end inked to identify its corresponding Z coordinate on the grid (apical/basal) and the corresponding X and Y (grid) coordinates recorded allowing generation of high resolution 3D histological maps of the prostate and the tumor burden. During the pilot, the process was burdensome and added unnecessary operative time as well as burden and costs to the pathology department. It required several individuals to be present during the biopsy to process the samples as the biopsy proceeds and the complexity added more time to the operative period. Also, the detailed pathology was becoming hard to process in our pathology department due to clinical workloads and cancer-waiting times were becoming long.

These constraints would have compromised our ability to process patients in the PROMIS pathway in a timely fashion and also

eventually not allow us to complete recruitment within the projected timelines. For the main phase we used the modified Barzell zonal anatomy of the prostate (which we used to plan procedures in the pilot phase) to divide the gland into 22 distinct anatomical zones. Cores from each zone were potted collectively. 5mm sampling was still undertaken.

Though conferring less spatial resolution, it was no less accurate than the approach employed in the pilot. It remains highly discriminative and informative in allocating areas of disease and assessing its burden as well as conveying enough information for the primary and secondary objectives of PROMIS and future research outcomes. Detailed standards of operation are attached in (*Appendix II*).

3.9.4. Histological analysis:

PROMIS biopsy samples were reported in accordance to a strict standard operating procedure (SOP) attached in (*Appendix II*). Blinding was maintained. Pathologists were not aware of any of the MRI results or any other aspect of the trial. They were only informed of the patient age and PSA value. Also, the TPM-biopsy and TRUS biopsy from individual patients were sent to different pathologists who reported them independently to minimize review and work-up biases.

All pathologists received training prior to site initiation on the details of the PROMIS SOP for reporting biopsy results. In all participating centres, the TRUS-biopsy samples were reviewed and reported by a PROMIS trained physician locally in the site of biopsy reflecting normal clinical practice. All TPM-biopsy samples were reviewed and reported centrally (University College London Hospital) pathology department by expert specialized uro-pathologists to maintain the quality and accuracy of the reference standard.

The PROMIS histological analysis is unprecedented in the level of detail most notably, in the analysis of the reference standard. Pathologists reported several parameters on a core-by-core basis for both TRUS-biopsy and TPM-biopsy. They reported primary, secondary and tertiary Gleason scores identified in each core and whether there was perineural or lymphatic invasion. They also reported the presence of high-grade prostatic intraepithelial neoplasia, atypical small acinar proliferation, and inflammation.

Also, the pathologist calculated and reported the cancer core length (CCL), which is the length of area harboring cancer in each biopsy core in two different methods¹¹⁸ as there is no consensus with respect to which is the best method to define the

CCL when discontinuous foci of cancer are present within the same core. Based on a recent survey, half of the pathologists consider that intervening benign tissue is not part of the cancer (separate count), whereas the remaining half count CCL from the initial part of the core with cancer to the end of the last cancer foci, regardless of the amount of benign tissue in between (cumulative count) ¹¹⁹.

Results were plotted on a visual map with color-coding to reflect the risk stratification derived from each core (Figures 3.4 and 3.5) ⁹². This reporting format presents unprecedented detailed clarity in recording the spatial position and relationship between positive cores, their Gleason grades and estimated lesion volumes.

3.9.4.1. Changes in histological analysis in the main phase

During the PROMIS pilot phase, each core from the TPM samples was an inked, stained and related grid coordinate recorded as described in (*section 3.9.3*). Pathologists assigned core-by-core risk stratification to tabular and visual reports depicted in (*figure 3.4*). Unfortunately during the pilot it became evident that this approach was causing significant burdens on the conduct of the biopsy procedure (*section 3.9.3.1*) and pathology processing time. The need to maintain the accuracy and the order of the coordinates during processing was significantly time

consuming and costly and was causing unacceptable delays in delivering the results to the patient.

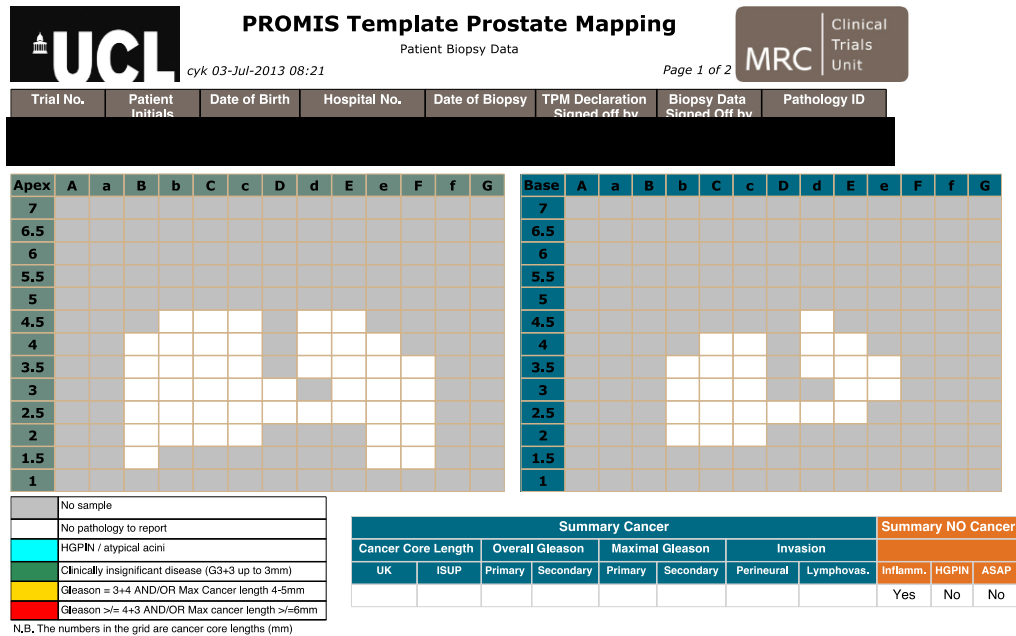


Figure 3.4: TPM results for a patient recruited to the pilot phase.

For the main phase we adopted a less complex approach by dividing the prostate into 20 separate zones according to a modified barzell classification and potting the cores according to their zonal locations. Pathologist produced detailed and pictorial reports to the level of a single zone rather than a single core as in the pilot as shown in (Figure 3.5).

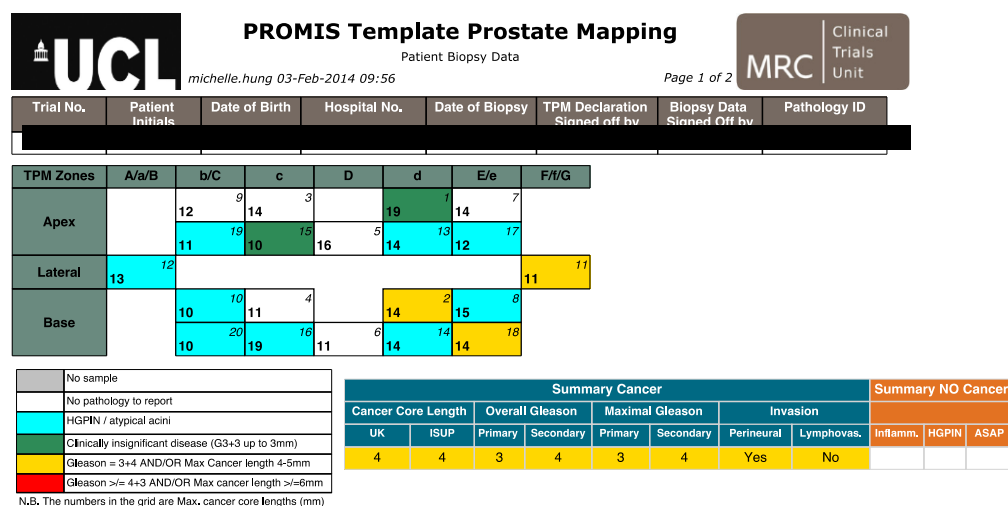


Figure 3.5: TPM results for a patient recruited to the main phase

3.9.5. Definitions of clinically significant disease

As discussed in (Section 2.4), there are no widely accepted definitions of clinically significant cancer. The previous risk stratification criteria were based on TRUS biopsies and if applied to TPM-biopsies, the prevalence of intermediate and high risk disease would be artificially inflated given the different sampling densities between both biopsies^{120,121}.

The high resolution PROMIS histological analysis was designed to allow for assessment of findings against any proposed definition of significance. This gave us the opportunity to therefore analyze MP-MRI against several in the PROMIS results.

For the primary and secondary outcomes of PROMIS (*Section 3.6*), we used defined criteria previously developed and validated for use with TPM-biopsy. Known as the UCL criteria⁹², which calculate the dominant Gleason pattern as the most frequent pattern in a sample (rather than the highest grade). It also uses the cancer core length (CCL) as a predictor for the volume of the lesion^{92,122-124}.

For the primary outcome, the definition of clinical significance was set as cancer core involvement $\geq 6\text{mm}$ and/or Gleason $\geq 4+3$ or the presence of any Gleason pattern ≥ 5 (Definition 1) in any location. This cancer core length in particular relates to an area of cancer on TPM biopsies that approximates to a lesion volume of $\geq 0.5\text{ml}$ ³³.

This was chosen as the primary outcome on the basis that few physicians would disagree that any man with this burden of cancer would require treatment. A secondary definition of clinically significant disease was also used (cancer core length $\geq 4\text{mm}$ and/or Gleason $\geq 3+4$) in any location (Definition 2).

The same definitions of significance were used with the TRUS biopsy results. For MP-MRI, a score of ≥ 3 to indicate a positive MRI result was used.

3.9.6. Translational research objectives

PROMIS was an ideal setting for assessing the utility of biomarkers (from urine and blood) to identify men with clinically significant prostate cancer. It is, to our knowledge, the first time that a broad spectrum of men at risk have been evaluated using a gold standard reference biopsy technique that accurately characterizes the presence, size and grade of prostate cancer.

A comprehensive bank of tissue samples (serum, plasma, germ-line DNA, urine) was collected from men prior to biopsy, to analyse urinary and serum biomarkers with respect to the detection of clinically significant prostate cancer on TPM-biopsy. These subsequent analyses will be reported at a later date but were not carried out at the time of writing my thesis.

3.9.7. Sample size calculation

Power calculations were performed in relation to: (1) Precision around the estimates for the accuracy of MP-MRI relative to TPM-biopsy in terms of the primary definition of clinically significant cancer, (2) a head-to-head comparison of MP-MRI versus TRUS-biopsy, and (3) an assumed underlying prevalence of clinically significant cancer by the primary definition of

15%.^{36,37,120,125}. for the less stringent definition (definition 2) it was assumed that 25% would have clinically significant prostate cancer as detected by the reference standard.

The largest sample size obtained from the power calculations around (1) and (2) above was 714 (detailed below), and this was taken as the maximum number of men required to have all three tests (MP-MRI, TPM-biopsy and TRUS-biopsy), based on the assumption that MP-MRI and TRUS-biopsy are uncorrelated.

Regarding precision (1), assuming a specificity of 77%, in order to demonstrate that the lower 95% confidence interval is at least 70%, we would require 407 cases of clinically insignificant prostate cancer. This is equivalent to a total of 479 men for definition 1 and 543 men for definition 2. Assuming a sensitivity of 75%, in order to demonstrate that the lower 95% confidence interval for sensitivity is at least 60%, we would require 97 cases of clinically significant prostate cancer. This is equivalent to a total of 647 men for definition 1 and 388 for definition 2. These estimates of sensitivity and specificity were considered realistic based on the literature available at the time^{126,127}. 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.

Regarding MP-MRI VS TRUS biopsy (2), It was assumed that TRUS-biopsy detects 48% of clinically significant prostate cancers^{120,128} and that MP-MRI would detect at least 70%; these were conservative estimates. Using McNemar's test for paired binary observations,¹²⁹ 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 1 and 428 men for definition 2. (*Table 3.5*) shows the required sample size for the McNemar test for different levels of agreement between MP-MRI and TRUS. 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 is very unlikely but is included for completeness.

	TRUS result (for true cases)*				Required no. cases**	Required sample size	
	Negative		Positive			Prevalence 15% DEFINITION ONE	Prevalence 25% DEFINITION TWO
MF-MRI results	-ve	+ve	-ve	+ve			
Sensitivity = 70%	0.29	0.23	0.01	0.47	48	321	192
Independence assumption†	0.25	0.27	0.05	0.43	66	441	264
	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

Table 3.5: required sample size for the McNemar test for different levels of agreement between MP-MRI and TRUS

The Independent Trial Steering Committee carried out an a priori interim review after 50 cases had had all three tests. Although a higher than anticipated prevalence of any cancer was observed, no changes were recommended to the target sample size.

3.9.8. **Statistical analysis plan**

All statistical analyses were performed according to a statistical analysis plan included in (*Appendix II*) which was agreed prior to inspection of the data. Stata Version 13.0 software (Stata Corporation, Texas, USA) was used to perform the analyses.

The analysis was based on all evaluable data, excluding men without all three test results and any data rejected as part of the external MP-MRI quality control/quality assurance process.

For each comparison, 2x2 contingency tables were used to present the results and calculate the diagnostic accuracy estimates with 95% confidence intervals. Given the paired nature of the test results, McNemar tests were used for the head-to-head comparisons of sensitivity and specificity between MP-MRI and TRUS-biopsy. Because the positive and negative predictive values (PPV and NPV, respectively) are dependent on disease prevalence, a general estimating equation logistic regression model was used to compare the PPV and NPV for MP-MRI and TRUS biopsy against TPM^{130,131}.

The sensitivities, specificities and predictive values were calculated for MP-MRI based on the overall radiological score for MP-MRI and the assessed definitions for clinically significant cancer on TPM-biopsy.

The format of the 2x2 table is shown in (*Table 3.6*). **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.

		MP-MRI		
		+ve	-ve	Total
TPM-biopsy	+ve	a	b	a+b
	- ve	c	d	c+d
	Total	a+c	b+d	

Table (3.6): 2 by 2 tables to demonstrate accuracy of MP-MRI with respect to TPM-biopsy

For the comparison of TRUS-guided biopsy and MP-MRI, McNemar's test was used to compare the agreement between MP-MRI (radiological score ≥ 3) and TRUS-biopsies (definition 1) in the subset of men found to have clinically significant prostate cancer according to definition 1 on TPM-biopsy. For the secondary analysis, all analyses performed for definition 1 were repeated for definition 2 on TPM-biopsy. At the request of *The Lancet* reviewers, where our main results were published, a post-hoc analysis for detecting and ruling out any Gleason score $3+4=7$ or more was also conducted.

Odds ratios represent the odds of each test correctly detecting the presence or absence of disease. Ratios were presented as TRUS-biopsy relative to MP-MRI, so ratios >1 favour TRUS-biopsy and ratios <1 favour MP-MRI.

4. Chapter 4: The *PROMIS* trial outcomes

4.1. Screening, recruitment and withdrawals

Recruitment took place between May 2012 and November 2015 across 11 NHS hospitals in England; University College London Hospital (lead centre), Basingstoke and North Hampshire Hospital, Imperial College/Charing Cross Hospital, Musgrove Park Hospital, Maidstone Hospital, Southmead Hospital, Whittington Hospital, Wrexham Maelor Hospital, Royal Hallamshire Hospital, Frimley Park Hospital, Southampton General Hospital.

Screening data was returned with adequate quality from the most active 6 of the 11 participating sites, registering 608 of the 740 registrations. In summary, 608/1618 (38%) of men screened at these centres were registered into the study. However, about half of the 1010 non-registered men were either ineligible according to the entry criteria (n=450) or there was a valid clinical reason for non-entry (N=68).

In 378 (37%) the reason for not registering was patient or clinician refusal, and 11 (1%) experienced delays before accessing the PROMS patient pathway but would have been eligible otherwise.

According to the baseline characteristics we were able to collect on these non-registered men, there were no strong differences in age or PSA between the 389 men who were either delayed or refused entry and those who consented to be registered into PROMIS.

A total of 740 participants were registered to the trial. (Figure 4.1) and (Table 4.1) detail the recruitment process across sites. Of the 740 men registered, 164 subsequently withdrew from the study before completing all three tests. Reasons for withdrawal are shown in (Table 4.2). Most withdrawals took place before the combined biopsy, and the most common reason for withdrawal was the discovery of a large prostate volume (>100 cc), which was a mandatory withdrawal criterion. A total of 576 men were included in the final analysis. For the analysis set, the median (range) time between MP-MRI and combined biopsy was 38 (1-190) days. Median time between registration and end-of-study visit was 111 days (range 31-421). (Figure 4.2) depicts patient flow through the PROMIS trial.

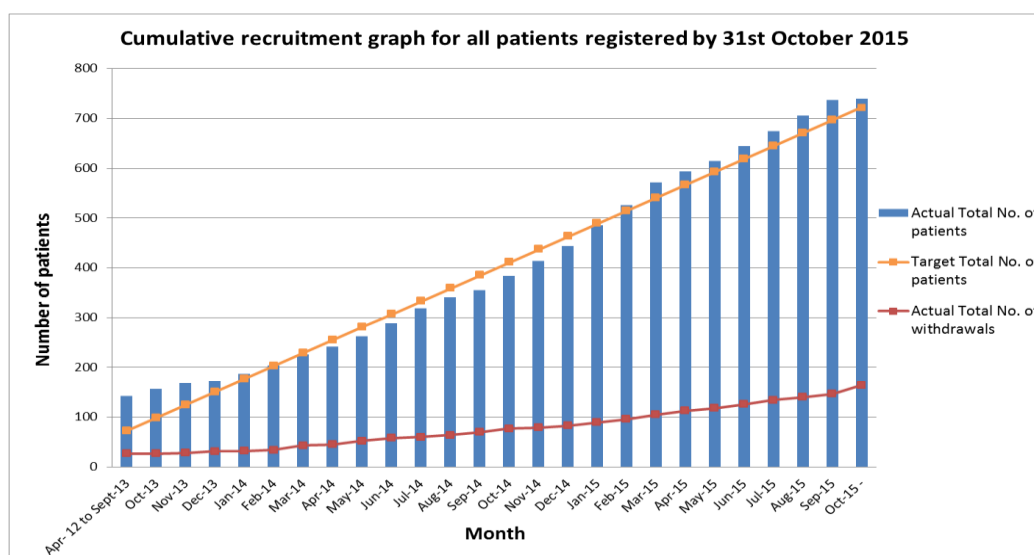


Figure 4.1: Cumulative recruitment graph for all registered men

Site	Date Activated	First patient recruited	Number of patients recruited	Number of patients withdrawn	Net recruited	% withdrawn
UCL	28/03/2012	17/05/2012	304	82	222	27%
Basingstoke	13/11/2012	04/02/2013	130	21	109	16%
Imperial College	20/09/2013	13/11/2013	41	10	31	24%
Musgrove Park	16/01/2014	17/01/2014	36	4	32	11%
Maidstone	20/02/2014	27/03/2014	12	1	11	8%
Southmead	25/02/2014	10/03/2014	44	5	39	11%
Whittington	17/04/2014	03/06/2014	18	11	7	61%
Wrexham	01/07/2014	18/07/2014	39	5	34	13%
Sheffield	01/09/2014	27/08/2014	36	4	32	11%
Frimley Park	25/09/2014	02/10/2014	25	5	20	20%
Southampton	10/11/2014	19/11/2014	55	16	39	29%
Total:			740	164	576	22%

Table 4.1: recruitment figures per individual participating sites

Timing of withdrawal					
Reason	Before MRI	Before CPB	During CPB	After CPB	Total
Ineligible	1	2	0	1	4
Unblinded	0	2	0	0	2
Large prostate	1	46	21	1	69
T4 or nodal disease	0	5	0	0	5
Clinical reasons*	5	15	0	1	21
Did not want biopsy	4	17	0	0	21
Did not want to wait - went private	1	4	0	0	5
No longer wished to participate	5	21	0	0	26
Other	0	10	0	1	11
Total	17	122	21	4	164

* Various reasons including cardiovascular events, renal/urological problems, other cancers.

Table 4.2: PROMIS withdrawals details

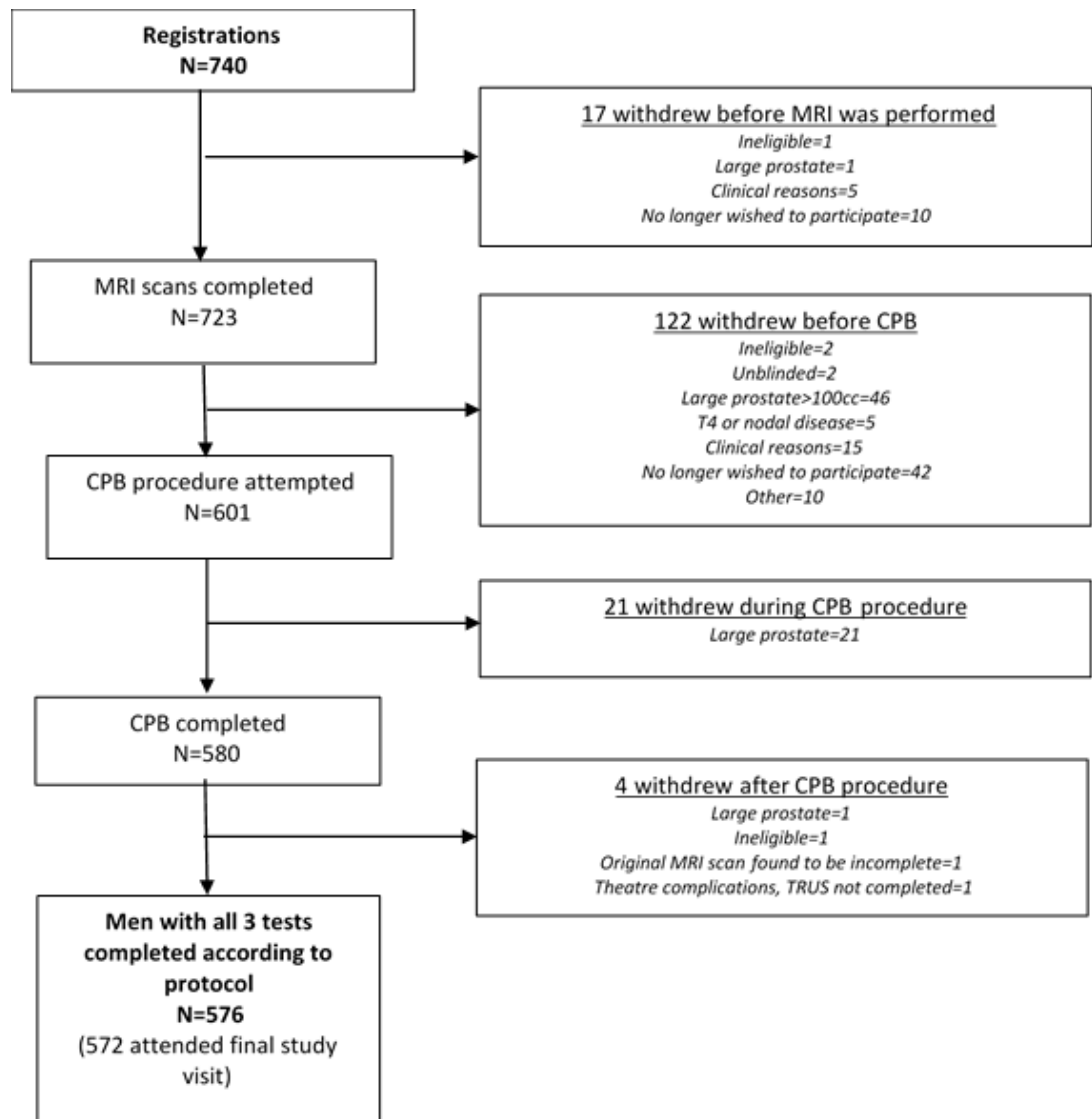


Figure 4.2: Flowchart showing status for all men screened and registered in PROMIS

Unblinding:

During the study there have been two cases of unblinding:

Case 1:

The clinician due to perform the combined prostate biopsy procedure saw the MP-MRI scan and report for a patient due for biopsy. The fundamental error associated with this case was that the patient's MRI scan was not marked as a research patient, therefore a radiologist not associated with the trial reported the scan and uploaded the results onto the NHS system. As the time between viewing the report and the scheduled biopsy was so short, another clinician could not be assigned to perform the biopsy. As a result, this patient was withdrawn from the study and biopsied according to local practice.

Case 2:

The patient was accidentally given the results from his MRI scan before the CPB procedure. This patient was also withdrawn from the study.

4.2. Trial timelines and data return

Data return from participating centres was deemed excellent by the TMG and our TSC/DMC. (Table 4.3) details data return figures. (Table 4.4) details the time lines from recruitment to conclusion of participation in PROMIS.

Trial Site	Total number of forms expected	Total number of forms received	Percentage received
Wrexham	290	290	100%
Imperial	282	282	100%
Maidstone	91	91	100%
Sheffield	272	271	99.6%
Basingstoke	940	935	99.5%
Musgrove Park	273	270	98.9%
Frimley Park	182	180	98.9%
Southmead	321	316	98.4%
Southampton	363	357	98.3%
Whittington	105	100	95.2%
UCLH	2121	2005	94.5%

Table 4.3: *Completeness of report forms across participating sites*

Time period	Mean in days (SD)	Median in days [Range]
<i>Pre-study</i>		
Between referral and registration (missing=0)	84 (137)	45 [0 to 1657]
<i>Within study</i>		
Between registration and MRI (missing=0)	29 (27)	26 [-5 to 346]
Between MRI and CBP (missing=5)	43 (27)	38 [1 to 190]
Between CBP and final visit (missing = 9)	42 (17)	40 [15 to 260]
<i>Total between registration and final visit (missing = 4)</i>	<i>114 (42)</i>	<i>111 [31 to 421]</i>

Table 4.4: *Time periods between tests for men participating in*

PROMIS.

4.3. Side effect profile and serious adverse events

Most men (88%) experienced at least one side-effect. Table 4.5 shows all documented side effects encountered throughout participation in PROMIS with an overall percentage.

<i>Side effect [Data un-returned]</i>	<i>Number (%)</i>
<i>MP-MRI</i>	
Pain/discomfort [15]	11 (2)
Allergic reaction to contrast medium [16]	1 (<1)
Other	3 (<1)
<i>Combined Prostate Biopsy Procedure</i>	
Pain/discomfort [13]	362 (64)
Dysuria [17]	256 (46)
Haematuria [11]	380 (67)
Haematospermia [51]	291 (55)
Erectile dysfunction (requiring medication, injection therapy or devices) [48]	76 (14)
Urinary tract infection (only if confirmed by a lab test) [11]	32 (6)
Systemic urosepsis [9]	8 (1)
Acute urinary retention [12]	58 (10)
Symptoms associated with general/spinal anaesthetic [43]	19 (4)
Other	65 (11)
<i>Total patients with any side effect [8]</i>	<i>501 (88)</i>

(Table 4.5) Occurrence of side effects after each test for the 576 patients who underwent all tests

Serious adverse events

A serious adverse event (SAE) is defined as any event that leads to death, life-threatening situation, in-patient hospitalisation, persistent or significant disability, congenital anomaly/birth defect, or other important medical condition¹³². There were 44 reports of SAE during the study. This equates to a risk of $44/740 = 5.9\%$ [95%CI 4.4–7.9]. Twenty-eight of the events (64%) involved the uro-genital system, and the most common events were urinary retention and urinary tract infections or urosepsis.

Ten cases of sepsis have occurred. Nine occurred after the combined biopsy procedure (CBP) during the study and one case of sepsis prior to the CPB and is not related to trial interventions. This equates to a post CPB risk of sepsis of $9/601 = 1.5\%$ [95% CI 0.7-2.8].

There were no deaths up to the time limit for reporting SAEs (30 days after last study visit). All SAEs and particularly sepsis cases were independently reviewed by the TSC/DMC to ensure that the rate of sepsis was not higher than expected from TRUS biopsy alone. No safety concerns were raised during these reviews.

4.4. Baseline characteristics of participants

(Table 4.6) details the patients' characteristics for the 576 men included in the final analysis and the 164 who withdrew after registration. It shows that withdrawals had similar age and PSA to the participants who completed the study.

<u>Characteristic [Data un-returned]</u>	<u>576 men included</u>	<u>164 withdrawals</u>
<u>Mean (SD) age, years [0]</u>	<u>63.4 (7.6)</u>	<u>64.5 (7.5)</u>
<u>White</u>	<u>502 (87)</u>	<u>136 (83)</u>
<u>Mixed</u>	<u>6 (1)</u>	<u>2 (1)</u>
<u>Asian or Asian British</u>	<u>16 (3)</u>	<u>5 (3)</u>
<u>Black or Black British</u>	<u>39 (7)</u>	<u>16 (10)</u>
<u>Other</u>	<u>12 (2)</u>	<u>4 (3)</u>
<u>Family history of prostate cancer, n (%) [7]</u>		
<u>Yes</u>	<u>127 (22)</u>	<u>27 (17)</u>
<u>No</u>	<u>442 (78)</u>	<u>130 (83)</u>
<u>Mean (SD) BMI, Kg/m² [62]</u>	<u>27.8 (4.4)</u>	<u>28.6 (5.2)</u>
<u>Mean (SD) PSA, ng/ml [0]</u>	<u>7.1 (2.9)</u> <u>Range 0.5 to 15</u>	<u>7.1 (2.7)</u> <u>Range 1.0 to 14.7</u>

(Table 4.6): characteristics of the included and withdrawn patients.

4.5. The index test (MP-MRI) findings

Data were available on Tesla strength in 574 of the 576 men. All 574 had a 1.5 tesla scan performed. For the 576 men included in the final analysis, the mean (\pm SD) volume of the prostate was 48 (\pm 20) cc. There were 6 men with prostate volumes of over 100cc as they were entered prior to this threshold being adopted as exclusion criterion. At a TMG meeting on 9th November 2015, it was decided that these 6 men should remain in the study as their TPM-biopsies were of high standard.

The distribution of MRI scores for any cancer overall, the primary MRI outcome (definition 2: ≥ 0.2 cc and/or $\geq 3+4$), the secondary MRI outcome (definition 1: ≥ 0.5 cc and/or $\geq 4+3$) and the tertiary MRI outcome (dominant Gleason 4) are presented in (*Table 4.7*).

For the primary and secondary outcomes for MRI score, two analyses have been performed, one that uses an MRI score of ≥ 3 to indicate a positive MRI result and another that uses a cut off of ≥ 4 to indicate a positive MRI result.

MRI score	<u>Any cancer overall</u>	<u>Primary MRI outcome</u> Definition 2: ≥0.2cc and/or ≥3+4	<u>Secondary MRI outcome</u> Definition 1: ≥0.5cc and/or ≥4+3	<u>Tertiary MRI outcome</u> Dominant Gleason 4
1=Highly likely benign	2 (<1%)	23 (4%)	75 (13%)	132 (23%)
2=Likely benign	101 (17%)	135 (23%)	186 (32%)	212 (37%)
3=Equivocal	197 (34%)	163 (29%)	139 (24%)	154 (26%)
4=Likely malignant	132 (23%)	120 (21%)	91 (16%)	56 (10%)
5=Highly likely malignant	144 (25%)	135 (23%)	85 (15%)	23 (14%)
TOTAL	576 (100%)	576 (100%)	576 (100%)	575 (100%)*

* Note – Dominant Gleason 4 score missing in 1 man

(Table 4.7): MRI scores for each MRI definition of cancer.

4.6. The standard test (TRUS biopsy) findings:

All TRUS biopsies were conducted as per PROMIS standard operating procedures and protocol after the TPM was conducted. No protocol breaches were reported with their conduct.

4.6.1. Any cancer

The prevalence of any cancer was $286/576 = 50\%$ [95% CI 45-54]. Of the 286 with cancer, 65 had peri-neural invasion and 1 had lympho-vascular invasion.

4.6.2. Primary outcome pathology definition 1

Pathology Definition 1: Dominant Gleason pattern ≥4 and/or

*Any Gleason pattern ≥5 and/or
Cancer core length ≥6mm*

The prevalence of clinically significant cancer was $124/576 = 22\%$ [95% CI 18-25]. Of the 124 with clinically significant cancer, 48 had peri-neural invasion and 1 had lympho-vascular invasion. (*Table 4.8*) summarizes the distribution of disease according to definition 1.

4.6.3. Secondary outcome pathology definition 2:

*Pathology Definition 2: Any Gleason pattern ≥ 4 and/or
Cancer core length $\geq 4\text{mm}$*

The prevalence of clinically significant cancer was $203/576 = 35\%$ [95% CI 31-39].

Of the 203 with clinically significant cancer, 63 had peri-neural invasion and 1 had lympho-vascular invasion. (*Table 4.8*) summarizes the distribution of disease according to definition 2.

Grades*	Any cancer N=286	Clinically significant according to definition 1 N=124	Clinically significant according to definition 2 N=203	Exploratory definition (Gleason ≥ 7) N=151
Mean (SD) cancer core length, mm	5.2 (4.1)	8.4 (4.3)	6.6 (4.1)	6.7 (4.4)
3+3	135	26#	52#	0
3+4	103	50#	103	103
3+5	1	1	1	1
4+3	34	34	34	34
4+4	6	6	6	6
4+5	4	4	4	4
5+3	1	1	1	1
5+4	2	2	2	2

Men classified as clinically significant on the basis of core length despite having low Gleason grades

(Table 4.8): *Distribution of cancer on TRUS biopsy pathology results.*

4.6.4. Other pathology:

290 men did not have cancer yet showed combinations of severe **inflammation** (n=99), **high-grade prostatic intraepithelial neoplasia** (n=61) and **atypical small acinar proliferation** (n=31).

4.7. Incidence and characteristic of cancer in study population: The reference standard (TPM) results

There were no reports of any CPB procedures being performed against protocol and for all 576 procedures the TPM-biopsy was completed before the TRUS-biopsy. The prevalence of disease according to several definitions is summarized in (*Table 4.9*)

TPM-biopsy (n = 576)	Prevalence, n (%) [95% CI]
Any cancer	408 (71) [67-75]
	PNI = 156
	LVI = 3
Clinically significant, primary definition (Gleason $\geq 4+3$ and/or cancer core length ≥ 6 mm)	230 (40) [36-44]
	PNI = 133
	LVI = 3
Clinically significant, secondary definition (Gleason $\geq 3+4$ and/or cancer core length ≥ 4 mm)	331 (57) [53-62]
	PNI = 155
	LVI = 3
Clinically significant, exploratory definition (Gleason ≥ 7)	308 (53) [49-58]
	PNI = 152
	LVI = 3

PNI, peri-neural invasion; LVI, lympho-vascular invasion

(Table 4.9): Prevalence of cancer on TPM stratified by definition of clinical significance.

4.7.1. Any cancer

The prevalence of any cancer was $408/576 = 71\%$ [95% CI 67-75]. Of the 408 with cancer, 156 had peri-neural invasion and 3 had lympho-vascular invasion.

4.7.2. Primary outcome pathology definition 1:

*Pathology Definition 1: Dominant Gleason pattern ≥ 4 and/or
 Any Gleason pattern ≥ 5 and/or
 Cancer core length $\geq 6\text{mm}$*

The prevalence of clinically significant cancer was $230/576 = 40\%$ [95% CI 36-44]. Of the 230 with clinically significant cancer, 133 had peri-neural invasion and 3 had lympho-vascular invasion. (*Table 4.10*) summarizes the distribution of disease according to definition 1.

4.7.3. Secondary outcome pathology definition 2:

*Pathology Definition 2: Any Gleason pattern ≥ 4 and/or
Cancer core length $\geq 4\text{mm}$*

The prevalence of clinically significant cancer was 331/576 = 57% [95% CI 53-62]. Of the 331 with clinically significant cancer, 155 had peri-neural invasion and 3 had lympho-vascular invasion. (Table 4.10) summarizes the distribution of disease according to definition 2.

(Table 4.11) presents the prevalence of disease by site from the TPM biopsy. Which appear to be similar across most sites.

Gleason grades*	Any cancer N=408	Clinically significant according to definition 1 N=230	Clinically significant according to definition 2 N=331	Exploratory definition (Gleason ≥ 7) N=308
Mean (SD) cancer core length, mm	6.3 (3.8)	9.1 (2.7)	7.4 (3.4)	7.5 (3.4)
3+3	100	10#	23#	0
3+4	252	164#	252	252
3+5	1	1	1	1
4+3	44	44	44	44
4+5	7	7	7	7
5+4	4	4	4	4

Men classified as clinically significant on the basis of core length despite having low Gleason grades

(Table 4.10): Distribution of cancer on TPM pathology results

(Table 4.11) presents the prevalence of disease by site from the TPM biopsy, which appears to be similar across most sites.

Site	TPM - any cancer	TPM - defn 1	TPM - defn 2
UCL	153/222 (69%)	91/222 (41%)	124/222 (56%)
Basingstoke	81/109 (74%)	44/109 (40%)	66/109 (61%)
Bristol Southmead	28/39 (72%)	13/39 (33%)	20/39 (51%)
Musgrove Park	21/32 (66%)	14/32 (44%)	16/32 (50%)
Imperial	18/31 (58%)	6/31 (19%)	17/31 (55%)
Wrexham	24/34 (71%)	15/34 (44%)	21/34 (62%)
Southampton	31/39 (79%)	23/39 (59%)	25/39 (64%)
Frimley Park	14/20 (70%)	8/20 (40%)	12/20 (60%)
Sheffield	26/32 (81%)	11/32 (34%)	20/32 (63%)
Maidstone	8/11 (73%)	2/11 (18%)	6/11 (55%)
Whittington	4/7 (57%)	3/7 (43%)	4/7 (57%)
Total	408/576 (71%)	230/576 (40%)	331/576 (57%)

(Table 4.11): Disease prevalence by site.

4.7.4. Other Pathology

168 men did not have cancer yet showed combinations of severe **inflammation** (n=145), high-grade prostatic intraepithelial neoplasia (n=60) and atypical small acinar proliferation (n=58).

5. Chapter 5: PROMIS primary outcome analysis

The quality of data in PROMIS allows multiple possible combinations of test results to compare according to various different definitions of disease significance. In this section, I detail the results for the primary outcome, which defines significant disease on TPM and TRUS biopsy as Dominant Gleason pattern ≥ 4 and/or Any Gleason pattern ≥ 5 and/or Cancer core length $\geq 6\text{mm}$ (DEFINITION 1) and on MP-MRI, any LIKERT score of ≥ 3 . I follow this with sections on the secondary outcomes using several other combinations of definitions and outcomes.

5.1. Primary outcome: diagnostic accuracy of TRUS biopsy compared with TPM under (Definition 1)

The diagnostic accuracy results for TRUS biopsy compared with TPM-biopsy are shown in a 2x2 calculation format (Table 5.1)

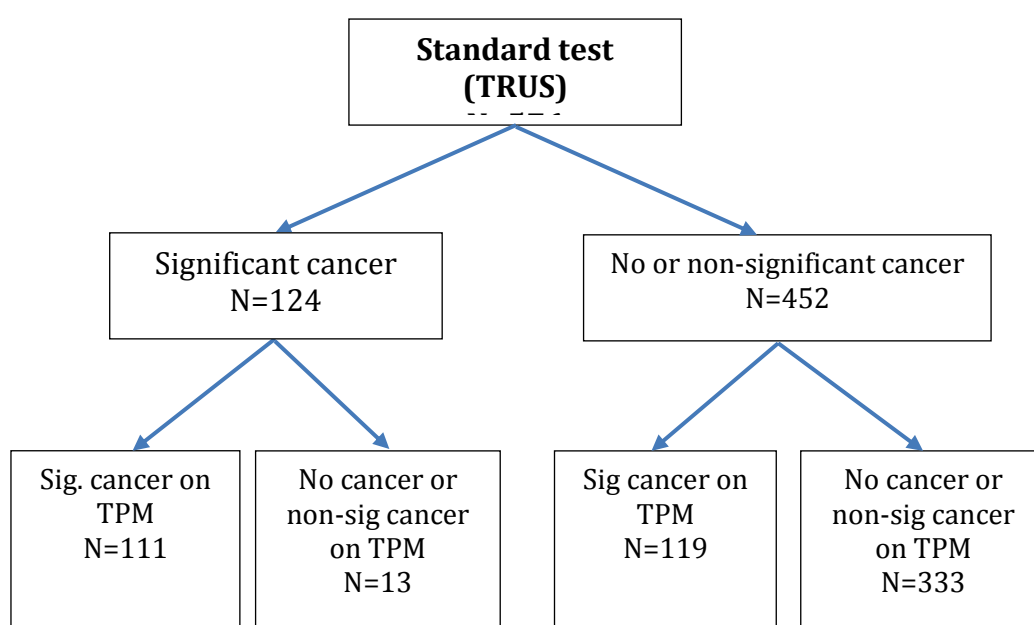
		TPM		
		+ Clinically significant	- No cancer or clinically non-significant cancer	Total
TRUS	+ Clinically significant	111	13	124
	- No cancer or clinically non-significant cancer	119	333	452
	Total	230	346	576

Sensitivity = 48% [95% CI 42-55]
Specificity = 96% [95% CI 94-98]

Positive predictive value = 90% [95% CI 83-94]
Negative predictive value = 74% [95% CI 69-78]

(Table 5.1): 2x2 calculation of TRUS biopsy accuracy versus TPM using DEFINITION ONE (Primary outcome)

This shows that if all patients (n=576) took only the standard test (TRUS biopsy), 119 patients (20.5%) would be falsely classified as free of significant cancer and may not receive timely, appropriate management. Also, 13 patients (2.25%) would be falsely classified as having significant disease and may receive inappropriate management with the associated side effects. All men had to endure the biopsy related side effect profile (Figure 5.1).



(Figure 5.1): TRUS Biopsy to TPM result comparison.

5.1.1. Summary of clinically significant cancer missed by TRUS

Biopsy:

- 7 cases of 3+3 with core lengths from 6-11mm
- 99 cases of 3+4 with core lengths from 6-14mm
- 13 cases of 4+3 with core lengths from 3-16mm

There were 13 patients with clinically significant (Definition 1) cancer on TRUS biopsies that were classified as negative or non clinically significant. As per the agreed statistical analysis plan, the TPM results were given precedence and the 13 men were classified according to their TPM findings.

5.2. Primary outcome: diagnostic accuracy of MP-MRI compared with TPM under (Definition 1)

The diagnostic accuracy results for MP-MRI compared with TPM-biopsy are shown in a 2x2 calculation format (*Table 5.2*). The sensitivity of MP-MRI for clinically significant (Definition 1, Primary outcome) cancer was 93% (95%CI 88-96) and NPV 89% (95%CI 83-94). The specificity of MP-MRI was 41% (95%CI 36-46) with PPV 51% (95%CI 46-56). (*Table 5.3*) and (*Figure 5.2*) depicts the distribution of the LIKERT score findings across patients and the prevalence of disease associated with each individual score as defined by Definition one (Primary outcome).

(*Table 5.3*) and (*Figure 5.2*) depicts the distribution of the LIKERT score findings across patients and the prevalence of disease associated with each individual score.

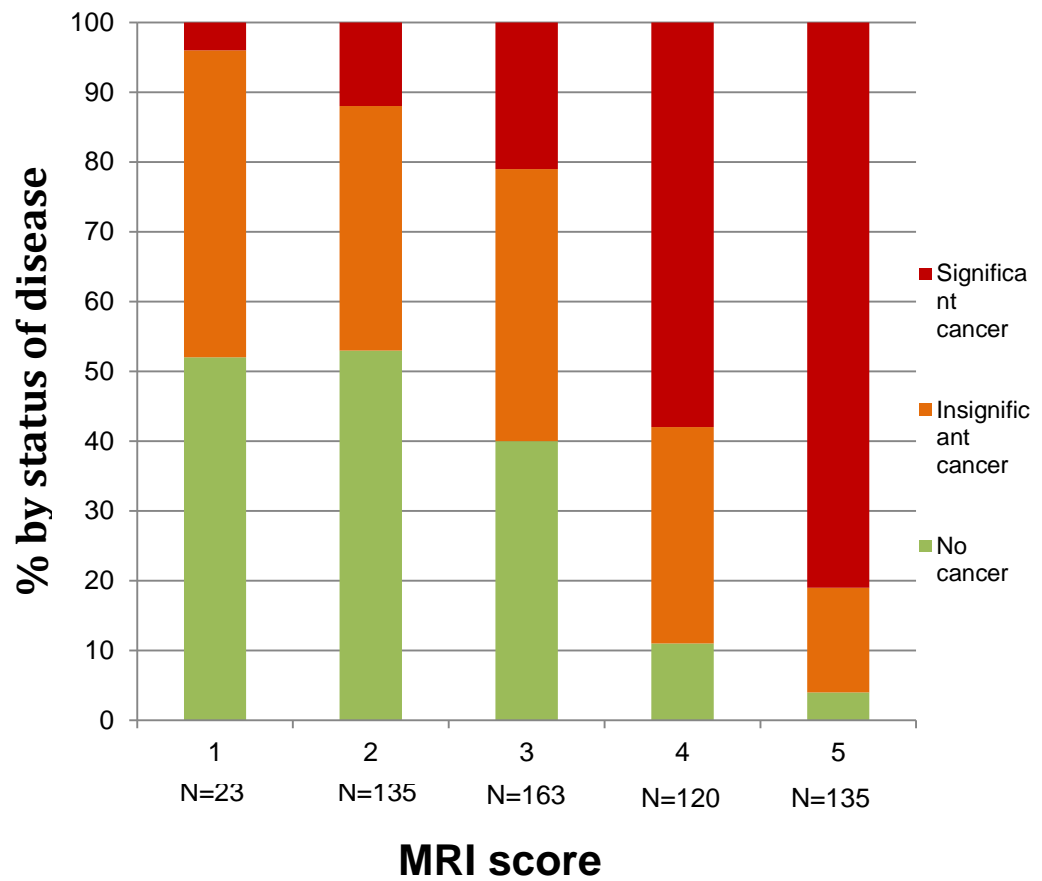
		TPM		
		+ Clinically significant	- Clinically non-significant	Total
MP-MRI	+ Clinically significant	213	205	418
	- Clinically non-significant	17	141	158
	Total	230	346	576

Sensitivity = 93% [95% CI 88-96] Positive predictive value = 51% [95% CI 46-56]
 Specificity = 41% [95% CI 36-46] Negative predictive value = 89% [95% CI 83-94]

(Table 5.2): 2x2 calculation of MP-MRI accuracy versus TPM using DEFINITION ONE (Primary outcome)

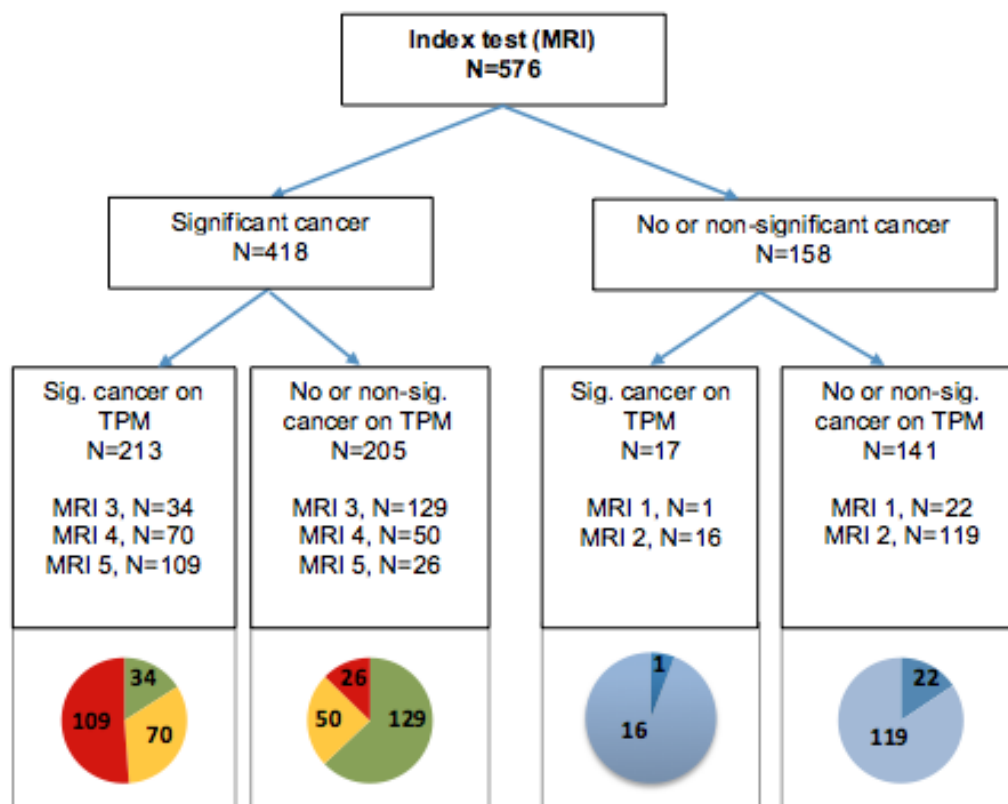
MRI score	Primary MRI score
1=Highly likely benign	23 (4%)
2=Likely benign	135 (23%)
3=Equivocal	163 (29%)
4=Likely malignant	120 (21%)
5=Highly likely malignant	135 (23%)
TOTAL	576 (100%)

(Table 5.3): Distribution of MRI scores across patients.



(Figure 5.2): Histological findings associated with the 1-5 LIKERT MP-MRI score. Significant cancer is set at Definition 1 (Primary outcome)

This shows that if all patients (n=576) took only the INDEX test (MP-MRI), only 17 patients (3%) would be falsely classified as free of significant cancer and may not receive timely, appropriate management. 205 patients (35. 5%) though would be falsely classified as having significant disease and may receive inappropriate management with the associated side effects (*Figure 5.3*). None of these patients would have been subjected to the side effects of a TRUS biopsy.



(Figure 5.3): MP-MRI to TPM result comparison.

5.2.1. Summary of clinically significant cancer missed by MP-MRI

MP-MRI identified 158 men as potentially not needing a biopsy (27% of total) of which, 17 cases (3% of total) harboring significant cancer (Definition 1) were missed:

- 1 case of 3+3 with a core length of 8mm
- 16 cases of 3+4 with core lengths from 6-12mm

5.3. Primary outcome: Head to head comparison of diagnostic accuracy of MP-MRI and TRUS-biopsy compared to TPM-biopsy:

Without considering the TPM results, (*Table 5.4*) details the number of discordant pairs between the MP-MRI and TRUS biopsy (Definition one Primary outcome) results. The proportion of discordant pairs is $(303+9)/576 = 54\%$.

		TRUS biopsy		
		+ Clinically significant	- Clinically non-significant	Total
MP-MRI	+ Clinically significant	115	303	418
	- Clinically non-significant	9	149	158
	Total	124	452	576

(Table 5.4): Agreement between MP-MRI and TRUS biopsy (Definition 1) for detection of clinically significant cancer (without comparison to TPM).

For head to head comparison of TRUS biopsy and MP-MRI using TPM as a reference standard, McNemar's test was used to compare Sensitivity and specificity.

For comparing positive and negative predictive values, McNemar's test is not suitable as both parameters are correlated to disease prevalence; a generalized estimating equation (*GEE*) logistic regression mode was used instead to produce odds ratios. Odds ratios represent the odds of each test correctly detecting the presence or absence of disease. For specificity and NPV, the coding logic is reversed, as the correct test result is a negative test result. Ratios are presented as TRUS relative to MP-MRI so ratios >1 favor TRUS and ratios <1 favor MP-MRI. (*Table 5.5*) details the results of the comparison.

TPM-biopsy definition of clinical significance	Prevalence of disease on TPM, N (%) [95% CI]	Test attribute	MP-MRI, % [95% CI]	TRUS-biopsy, % [95% CI]	Test Ratio* [95% CI]	p-value
Primary Definition (Gleason $\geq 4+3$ and/or cancer core length $\geq 6\text{mm}$)	230 (40% [36-44])	Sensitivity	93 [88-96]	48 [42-55]	0.52 [0.45-0.60]	$p < 0.0001$
		Specificity	41 [36-46]	96 [94-98]	2.34 [2.08-2.68]	$p < 0.0001$
		PPV	51 [46-56]	90 [83-94]	8.2 [4.7-14.3]	$p < 0.0001$
		NPV	89 [83-94]	74 [69-78]	0.34 [0.21-0.55]	$p < 0.0001$

* McNemar test to compare sensitivity and specificity present ratio of proportions;

General Estimating Equation (GEE) logistic regression model to compare PPV and NPV

present odds ratios. All ratios presented as TRUS biopsy relative to MRI.

(Table 5.5): Diagnostic accuracy of TRUS-biopsy and MP-MRI in the detection of clinically significant disease (Definition 1) using TPM as reference standard.

5.3.1. Comparison of significant cancers missed by both tests:

(Table 5.6) compares the histological characteristics on TPM-biopsy of clinically significant cases missed by MP-MRI and TRUS-biopsy

		MP-MRI Total = 17	TRUS biopsy Total = 119
Number (Range of maximum cancer core length)	Gleason 3+3	1 (8mm)	7 (6-11mm)
	Gleason 3+4	16 (6-12mm)	99 (6-14mm)
	Gleason 4+3	0	13 (3-16mm)

(Table 5.6): Histological comparison of significant cases missed by both tests

5.4. Summary of Primary outcome analysis

Sensitivity of MP-MRI for clinically significant cancer was 93% (95% CI 88–96%) and negative predictive value 89% (83–94%). Specificity of MP-MRI was 41% (36–46%) with positive predictive value 51% (46–56%). 158 (27%) of 576 men had a negative MP-MRI, of whom 17 had clinically significant cancer on TPM-biopsy. All 17 men had Gleason grade 3 + 4 or less with core lengths that ranged from 6–12 mm i.e., were considered significant only on basis of core length.

MP-MRI was more accurate than TRUS-biopsy in terms of both sensitivity (93% vs. 48%; McNemar test ratio 0.52 [95%CI 0.45-0.60]) and NPV (89% vs. 74%; GEE model estimate for odds ratio 0.34 [0.21–0.55], $p < 0.0001$). TRUS-biopsy demonstrated better specificity (41% vs. 96%; McNemar test ratio 2.34 [2.08-2.68], $p < 0.0001$) and PPV (51% vs. 90%; GEE model estimate for odds ratio 8.2 [4.7–14.3], $p < 0.0001$). The impact of these findings on the clinical pathway is discussed further in (*Chapter 8*).

6. Secondary outcome analysis

6.1. Diagnostic accuracy of TRUS-biopsy and MP-MRI for other definitions of clinically significant cancer

Diagnostic accuracy analysis for the secondary (any Gleason pattern ≥ 4 and/or Cancer core length ≥ 4 mm) and exploratory (any Gleason ≥ 4 regardless of core length) and several other definitions were conducted in the same manner as those for the primary outcome.

(*Table 5.1*) details the TPM findings, the diagnostic accuracy results for MP-MRI and TRUS biopsy compared to TPM (Sensitivity, Specificity, PPV and NPV) and the results of the head to head comparison based on those two definitions. (*Table 5.2*) shows the histological characteristics of cancers missed by TRUS-biopsy and MP-MRI for all histological definitions.

TPM definition of clinical significance	Prevalence of disease on TPM-biopsy, N (%) [95% CI]	Test attribute	MP-MRI, % [95% CI]	TRUS biopsy, % [95% CI]	Test Ratio* [95% CI]	p-value
Secondary Definition (Gleason $\geq 3+4$ and/or cancer core length $\geq 4\text{mm}$)	331 (57% [53-62])	Sensitivity	87 [83-90]	60 [55-65]	0.69 [0.64-0.76]	$p < 0.0001$
		Specificity	47 [40-53]	98 [96-100]	2.11 [1.85-2.41]	$p < 0.0001$
		PPV	69 [64-73]	98 [95-100]	22.7 [8.6-59.9]	$p < 0.0001$
		NPV	72 [65-79]	65 [60-70]	0.70 [0.52-0.96]	0.025
Any Gleason score 7 ($\geq 3+4$)	308 (53% [49-58])	Sensitivity	88 [84-91]	48 [43-54]	0.55 [0.49-0.62]	$p < 0.0001$
		Specificity	45 [39-51]	99 [97-100]	2.22 [1.94-2.53]	$p < 0.0001$
		PPV	65 [60-69]	99 [95-100]	40.8 [10.2-162.8]	$p < 0.0001$
		NPV	76 [69-82]	63 [58-67]	0.53 [0.38-0.73]	$p < 0.0001$

* McNemar test to compare sensitivity and specificity present ratio of proportions; General Estimating Equation (GEE) logistic regression model to compare PPV and NPV present odds ratios. All ratios presented as TRUS-biopsy relative to MRI.

(Table 6.1): Diagnostic accuracy of TRUS-biopsy and MP-MRI using alternative definitions of clinically significant cancer.

(Table 6.2) shows the histological characteristics of cancers missed by TRUS-biopsy and MP-MRI on those definitions compared to the primary definition.


Definition of significant	MP-MRI missed cases	TRUS-Biopsy missed cases
Primary n=230	<u>Total = 17</u>	<u>Total = 119</u>
	1 x Gleason 3+3 with core length 8mm	7 x Gleason 3+3 with core lengths 6-11mm
	16 x Gleason 3+4 with core lengths 6-12mm	99 x Gleason 3+4 with core lengths 6-14mm
	0 x Gleason 4+3	13 x Gleason 4+3 with core lengths 3-16mm
Secondary n=331	<u>Total = 44</u>	<u>Total = 132</u>
	6 x Gleason 3+3 with core lengths 4-8mm	18 x Gleason 3+3 with core lengths 4-11mm
	38 x Gleason 3+4 with core lengths 1-12mm	104 x Gleason 3+4 with core lengths 1-14mm
	0 x Gleason 4+3	10 x Gleason 4+3 with core lengths 3-16mm
Gleason ≥7 n=308	<u>Total = 38</u>	<u>Total = 159</u>
	38 x Gleason 3+4 with core lengths 1-12mm	146 x Gleason 3+4 with core lengths 1-14mm
	0 x Gleason 4+3	13 x Gleason 4+3 with core lengths 3-16mm

Table (6.2): Histological characteristics on TPM-biopsy of cases missed by MP-MRI and TRUS-biopsy using 3 definitions of clinically significant prostate cancer

For detection of any cancer regardless of grade or size, MP-MRI showed a *sensitivity* of 89% [95% CI 85-91], *specificity* of 33% [95% CI 26-41], a *PPV* of 76% [95% CI 72-80] and a *NPV* of 54% [95% CI 44-64]. TRUS biopsy showed a *sensitivity* of 68% [95% CI 63-72], a *specificity* = 95% [95% CI 90-98], a *PPV* of 97% [95% CI 94-99] and an *NPV* of 55% [95% CI 49-61].

On head to head comparison, MP-MRI showed better *sensitivity* (89% vs. 68%, McNemar test Odds ratio=0.18 [95% CI 0.11 - 0.30], $p<0.0001$) compared to TRUS biopsy. On comparing *specificity* (33% vs. 95%. McNemar test Odds ratio=0.04 [95% CI 0.01 - 0.10], $p<0.0001$) and *PPV* (76% vs. 97% Gee model odds ratio=9.55 [95% CI 4.96–18.38], $p<0.0001$). TRUS-biopsy showed significantly better results. For *NPV* (54% vs. 55%. Gee model odds ratio=1.02 [95% CI 0.72–1.45], $p=0.918$) there was no difference between both tests. (Table 6.3) demonstrates diagnostic accuracy of MP-MRI and TRUS tested using 27 different combinations of definitions of clinical significance.

SUMMARY OF DIAGNOSTIC ACCURACY		TPM		
		Any cancer	Path definition 1 (primary)	Path definition 2
MRI results Cut off ≥ 3	MRI Primary definition	Sens =82 Spec =50 PPV =80 NPV =53	Sens =93 Spec =41 PPV =51 NPV =89	Sens =87 Spec =47 PPV =69 NPV =72
MRI results Cut off ≥ 4	MRI Primary definition	Sens =58 Spec =89 PPV =93 NPV =46	Sens =78 Spec =78 PPV =70 NPV =84	Sens =66 Spec =85 PPV =86 NPV =65
TRUS biopsy results	Path Primary definition	Sens =30 Spec =100 PPV =100 NPV =37	Sens =48 Spec =96 PPV =90 NPV =74	Sens =38 Spec =100 PPV =100 NPV =54

 Green cells detail the primary outcome results.

(Table 6.3): Summary of diagnostic accuracy for different definitions of clinical significance.

6.2. Inter observer variability assessment

Inter-observer variability was assessed using blinded, double reporting of the same scan by 2 different radiologists. Reports from 2 radiologists at UCL have been completed independently for 132 paired scans and a LIKERT score of 1-5 assigned to each report. Scores 1-2 were considered as clinically non-significant and scores 3-5 as clinically significant.

For this group, agreement between radiologists for the detection of clinically significant cancer by the primary definition was 80. This corresponded to a kappa statistic of 0.5 (moderate agreement according to the Koch and Landau classification, where agreement is

graded from excellent ($\kappa \geq 0.80$), good (0.60–0.79), moderate (0.40–0.59), poor (0.20–0.39) to very poor (<0.20 .) Kappa statistics indicate how much better the agreement is over that which would have occurred by chance (the expected agreement). This is shown in (Table6.4).

MP-MRI score		Radiologist 2					
		1	2	3	4	5	Total
Radiologist 1	1	0	4	1	0	0	5
	2	0	19	15	0	0	34
	3	0	9	33	5	0	47
	4	0	1	10	7	5	23
	5	0	0	0	1	22	23
	Total	0	33	59	13	27	132

Expected Agreement	Agreement	Kappa	p-value
65%	33%	0.48 (Moderate)	<0.001

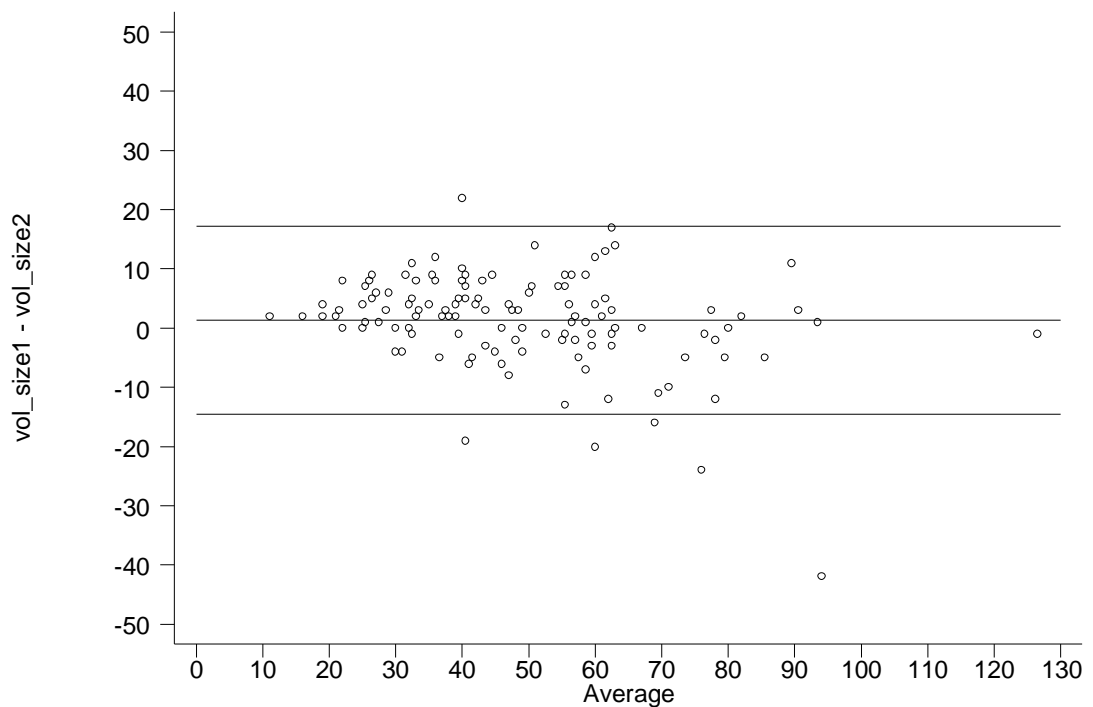
* Bold indicates perfect agreement between radiologists; Blue indicates agreement in terms of our primary outcome cut-off; yellow indicates disagreement in terms of our primary outcome cut-off.

(Table6.4): Assessment of inter-observer variability as per primary outcome.

For this group, agreement between radiologists on measurement of prostate volume was assessed using the Bland-Altman method, which plots the difference between measurements against the average of the measurements as shown in (Figure 6.1). Overall, the mean difference between volumes is +1.3cc [95%CI -0.04 to +2.69].

The limits of agreement demonstrate that 95% of the differences between measurements lie between -14.5 and +17.2cc.

(Figure 6.1) also demonstrates that there is a tendency for poorer agreement with larger volumes and this association is significant according to Pitman's test as well as simple linear regression. The plot indicates that the inter-observer reproducibility between radiologists for prostate volume measurement was approximately $\pm 15\text{cc}$.



Bland-Altman comparison of vol_size1 and vol_size2
Limits of agreement (Reference Range for difference): -14.518 to 17.169
Mean difference: 1.326 (CI -0.038 to 2.690)
Range: 11.000 to 126.500
Pitman's Test of difference in variance: $r = -0.317$, $n = 132$, $p < 0.0001$

(Figure 6.1): Bland-Altman plot for volume measurements between 2 radiologists.

6.2.1. Comparison of diagnostic accuracy between central (UCH) and non-central (non-UCH) sites

We wanted to determine whether the lead trial site (which was arguably the most experienced and responsible for training all other sites) demonstrated different diagnostic accuracy from the other sites to further assess the variations in diagnostic accuracy in different practice settings. Tables 6.5 and 6.6 indicate the results are almost identical.

		TPM		
		+ Clinically significant	- Clinically non-significant	<i>Total</i>
MP-MRI	+ Clinically significant	85	75	160
	- Clinically non-significant	6	56	62
	<i>Total</i>	91	131	222

Sensitivity = 93% [95% CI 86-98]

Specificity = 43% [95% CI 34-52]

PPV = 53% [95% CI 45-61]

NPV = 90% [95% CI 80-96]

(Table 6.5): Diagnostic results for MP-MRI for UCH site alone (Primary outcome)

		TPM		
		+ Clinically significant	- Clinically non-significant	Total
MP-MRI	+ Clinically significant	128	130	258
	- Clinically non-significant	11	85	96
	Total	139	215	354

Sensitivity = 92% [95% CI 86-96]

Specificity = 40% [95% CI 33-46]

PPV = 50% [95% CI 43-56]

NPV = 89% [95% CI 80-94]

(Table 6.6): Diagnostic results for MP-MRI for non-UCH site only (Primary outcome)

6.3. Health-related quality of life outcomes:

Participants filled in EQ-5D-3L questionnaires at enrolment, after MP-MRI, after the combined biopsy procedure and at the end of the study, which was on average 42 days after the combined biopsy procedure.

As part of the economic evaluation, the EQ-5D-3L profiles were converted into preference-based index scores using the UK tariff¹³³.

The index scores after each test were compared to their value at enrolment. There was no evidence of a change in index score between post MP-MRI and baseline (change=0.008; 95%CI -0.002 to 0.018).

However, an expected large and statistically significant negative impact after the combined biopsy procedure, with a change of -0.176 (95%CI -0.203 to -0.149) was not surprisingly seen.

7. Chapter 7: The concordance between the volume hotspot and the grade hotspot: a 3-D reconstructive model using the pathology outputs from the PROMIS trial

After conclusion of the pilot phase, the level of accuracy of the histological data collected allowed for a unique assessment of the heterogeneity of prostate cancer grades and sizes within the PROMIS histological TPM data set.

The accuracy and spatial resolution of the data allowed for a novel assessment of the previously unchallenged assumption that a biopsy directed at the longest dimension of a given lesion would capture the highest Gleason score. Some have raised concerns that this strategy may not be optimal^{134,135}. Instead, it has been argued that information acquired from imaging can identify a particular area to target in order to obtain the most aggressive component of one lesion, which may not be represented on targeting the longest dimension.

For this purpose, In this study, we attempted to assess the validity of the premise that the largest dimension of a tumour (termed “volume hotspot”) harbours the highest Gleason grade (termed “Gleason grade hotspot”)¹¹⁸.

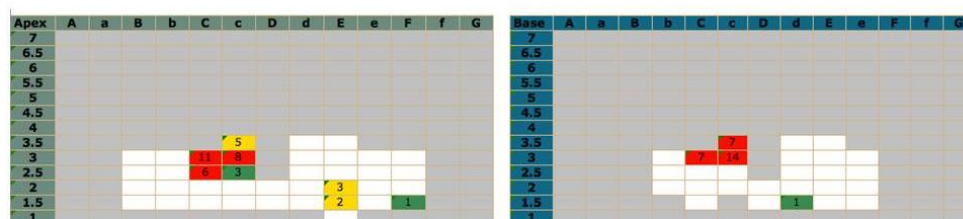
7.1. Patients and methods

For the purpose of this work, we have used the histological outputs from TPM biopsies conducted within the pilot phase of the trial. The pilot phase was unique in permitting such an analysis as each individual core was potted, processed and reported (*Figure 7.1*) separately as well as oriented in space (cranio-caudal (z) and x-y planes) as detailed in *Appendix II*.

APEX														BASE													
Core	Len	Can cer	Cancer (mm)	ISUP Len	Dist. Ink	1 Gleas	2 Gleas	3 Gleas	Peri Inv	Lymph Inv	Inflam	HG PIN	ASAP	Len	Can cer	Cancer (mm)	ISUP Len	Dist. Ink	1 Gleas	2 Gleas	3 Gleas	Peri Inv	Lymph Inv	Inflam	HG PIN	ASAP	
C 3	14	Yes	11	11	3	3	4	N/A	Yes	No				15	Yes	7	8	0	3	4	N/A	No	No				
C 2.5	12	Yes	6	6	4	3	3	N/A	Yes	No				8	No												
C 3.5	13	Yes	5	5	99	3	4	N/A	No	No				20	Yes	7	10	0	3	3	N/A	No	No				
C 3	11	Yes	8	8	3	3	4	N/A	No	No				19	Yes	14	14	0	3	4	N/A	No	No				
C 2.5	18	Yes	3	3	99	3	3	N/A	No	No				9	No												
d 1.5	9	No												12	Yes	1	1	9	3	3	N/A	No	No				
E 2	14	Yes	3	3	4	3	4	N/A	No	No				9	No												
E 1.5	7	Yes	2	2	1	3	4	N/A	No	No				10	No												
F 1.5	8	Yes	1	1	5	3	3	N/A	No	No																	

a

TPM full report



b

TPM visual report

(Figure 7.1): TPM histological findings per patient within the PROMIS trial: A full report and a visual report. In the full report (a), each core is labelled per coordinate and the following details are displayed: core length, cancer status, cumulative and separate cancer core length, cancer position, primary, secondary and tertiary Gleason grade, perineural and lymphovascular invasion as well as presence of inflammation, high-grade PIN and ASAP. The TPM visual report (b) provides immediate zonal location within the gland. Maximum cancer core length and colour coded risk attribution are displayed per coordinate with white boxes representing prostate biopsies with no cancer.

7.1.1. Histological definitions:

Several definitions were devised in order to conduct this analysis including:

Volume hotspot: Is the coordinate in which if a biopsy needle is deployed it will sample the largest dimension of the lesion and return the longest cancer core length. The relationship between lesion volume and cancer core length is well demonstrated in ⁹² previous publications and it is the basis of the lesion volume interpolation.

It is determined across the sampling plane (cranio-caudal) of a template biopsy rather than on maximum dimension of the lesion, which may not be accessible in a biopsy approach hence will not contribute to risk stratification.

Calculation of cancer core length (CCL):

There is no consensus with respect to which is the best method to define the CCL when non-continuous foci of malignancy are found within the same core. Based on a recent survey around half pathologists consider that intervening benign tissue is not part of the cancer (separate count), whereas the remaining half count CCL from the initial part of the core with cancer to the end of the last malignant focus, regardless of the amount of benign tissue in between (cumulative count) ¹¹⁹. We used separate counts within our primary analysis but also secondarily evaluated the impact of using the cumulative count.

Gleason hotspot: is the coordinate in which if a biopsy is deployed, it will capture the highest Gleason grade in the lesion independent of the overall lesion volume or Gleason score.

A homogenous lesion is defined as a lesion comprised of only one Gleason pattern and hence, both Gleason and volume hotspots are inherently concordant.

A heterogonous lesion is defined as a lesion composed of more than one Gleason pattern and hence the volume and Gleason grade hotspots may not be at the same biopsy coordinates (non-Concordance).

On reporting biopsies, primary and secondary Gleason grade are reported on the basis of relative percentage rather than on fixed quantitative thresholds. Therefore, in the case of one lesion generated

by the combination of various cores with the same total Gleason scores (ex: Gleason 7) but different amounts of each grade pattern per core (ex: Gleason 3+4, 30% grade 4), it is difficult to determine whether there is or there is not total Gleason score heterogeneity.

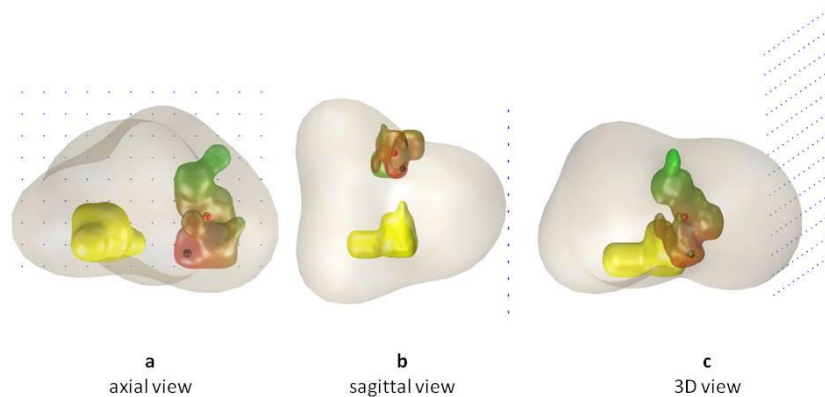
For the primary analysis, we considered the presence of Gleason 3+4 and Gleason 4+3 in different areas of the same constitutes heterogeneity, as there is some evidence that such a differentiation matters ¹³⁶.

For secondary analyses we also assumed heterogeneity within one lesion was present only when different total Gleason scores were present on biopsy. Meaning that Gleason 4+3 and Gleason 3+4 within the same lesion were considered homogeneous.

7.1.2. 3-dimensional models interpolation:

The 3-D disease models (Figure 7.2 a-b-c) were reconstructed using the detailed results enabling the creation of a 3-D map which potentially has 13 x 13 x 40 sections of pathological results (in terms of Gleason scores), as 13x13 (5mm) template grid holes are combined with two (apex and base) needle lengths of 20mm.

Individual lesions were delineated on the reconstructed 13x13x40 map by using the rule of 26 connectivity. Meaning that any group of positive cores are connected to 26 potential neighbour blocks to form a single lesion. This map was then further reconstructed into a finer spatial resolution (0.5x0.5x0.5mm³) by linear interpolation followed by a Gaussian smoothing, whose single parameter of isotropic variation was tuned so that the original histology results when re-sampled at the same template grid sites will be preserved.



(Figure 7.2 a, b and c): disease maps showing two different lesions within the same patient. One lesion (right side of the prostate; yellow) shows homogeneous grade; therefore, the hotspots are considered concordant. The second lesion (left side of the prostate; scale of colours) shows grade heterogeneity with the Gleason grade hotspot located in the inferior right side of the lesion; therefore, the hotspots are considered discordant.

Biopsy simulations were performed on the reconstructed models to acquire cancer core lengths and Gleason scores and determine their concordance. An animation of this modelling is available at <https://sites.google.com/site/yipenghu/gallery/template-biopsy-animation>

7.2. Results

94 were included in the present study. Median age was 62 years (IQR= 58-68) and median PSA was 6.5ng/ml (4.6-8.8). A median of 80 cores (69-89) were taken per patient with a median of 4.5 positive cores (0-12). Median maximum cancer core length (MCCL) was 3mm, both when using a cumulative (0-8) and a separate (0-7) CCL count. An example of a TPM report is given in (figure 7.1).

Primary analysis:

195 separate lesions were detected (*table 7.1*). Overall prevalence of homogeneous lesions was 148 (95%CI 76% \pm 6.0%). Most of these lesions had a Gleason score 3+3 (n=119; 61% \pm 6.9%), fewer had a Gleason score 3+4 (n=66; 34% \pm 6.6%), and a minority a Gleason score 4+3 (n=10; 5% \pm 3.1%). Median lesion volume was 0.075cc (0.025-0.225). Discordant hotspots were present in 11/47 (23% \pm 12.1%). The median 3-D distance between the hotspots when they were discordant was 12.8mm (9.9-15.5).

Overall, considering both homogeneous and heterogeneous lesions together, 184/195 (94% \pm 3.2%) of lesions harboured the Gleason grade hotspot in the volume hotspot.

Variable	Primary Analysis	Secondary Analysis		
Definitions of CCL and heterogeneity	Separate count / Gleason grades	Separate count / Gleason score	Cumulative count / Gleason grades	Cumulative count / Gleason score
No Independent lesions	195	195	190	190
Gleason Score, no (\pm 95% CI) 3+3 3+4 4+3	119 (61% \pm 6.9%) 66 (34% \pm 6.6%) 10 (5% \pm 3.1%)	119 (61% \pm 6.9%) 66 (34% \pm 6.6%) 10 (5% \pm 3.1%)	118 (62% \pm 6.9%) 64 (34% \pm 6.7%) 8 (4% \pm 2.9%)	118 (62% \pm 6.9%) 64 (34% \pm 6.7%) 8 (4% \pm 2.9%)
Lesion Volume, cc, median IQR Range	0.075 (0.025 - 0.225) (0.025 - 6.200)	0.075 (0.025 - 0.225) (0.025 - 6.200)	0.075 (0.025 - 0.275) (0.025 - 8.275)	0.075 (0.025 - 0.275) (0.025 - 8.275)

Homogeneous lesions, no. ($\pm 95\%$ CI)	148 (76% \pm 6.0)	152 (78% \pm 5.8%)	144 (76% \pm 6.1%)	148 (78% \pm 5.9%)
Heterogeneous lesions, no. ($\pm 95\%$ CI)	47 (24% \pm 6.0%)	43 (22% \pm 5.8%)	46 (24% \pm 6.1%)	42 (22% \pm 5.9%)
Heterogeneous Lesions with concordant hotspots, no. ($\pm 95\%$ CI)	36/47 (77% \pm 12.1%)	33/43 (77% \pm 12.6%)	34/46 (74% \pm 12.7%)	33/42 (79% \pm 12.4%)
Heterogeneous Lesions with no concordant hotspots, no. ($\pm 95\%$ CI)	11/47 (23% \pm 12.1%)	10/43 (23% \pm 12.6%)	12/46 (26% \pm 12.7%)	9/42 (21% \pm 12.4%)
3D Hotspots Distance in heterogeneous non concordant lesions, mm, median (IQR)	12.8 (9.9 - 15.5)	12.5 (9.9 - 15.8)	11.5 (9.9 - 14.0)	9.9 (9.8 - 15.3)
Total number of concordant lesions ($\pm 95\%$ CI)	184/195 (94% \pm 3.2%)	185/195 (95% \pm 3.1%)	178/190 (94% \pm 3.5%)	181/190 (95% \pm 3.0%)

(Table 7.1): Interpolation analysis results.

Secondary analyses:

Discordant hotspots were present in 10/43 (23% \pm 12.6%); the median 3-D distance between hotspots when they were discordant was 12.5mm (9.9-15.8).

When the histology outputs were reconstructed to determine the 3-D models using the cumulative method to assign CCL, 190 independent lesions were found (table 8.1). Most of these lesions had a Gleason score 3+3 (n=118; 62% \pm 6.9%), few showed a Gleason score 3+4 (n=64; 34% \pm 6.7%), and a minority a Gleason score 4+3 (n=8; 4% \pm 2.9%). Median lesion volume was 0.075cc (0.025-0.275). Between 144 (76% \pm 6.1%) and

148 (78% \pm 5.9%) lesions were considered homogeneous, according to the definition of grade heterogeneity used. Of the remaining heterogeneous lesions, 33/42 (79% \pm 12.4%) and 34/46 (74% \pm 12.7%) had Gleason grade hotspots that were concordant to the volume hotspots.

The median 3-dimensional distance in the discordant lesions was 9.9mm (9.8-15.3) and 11.5mm (9.9-14), respectively.

The overall concordance rates of all secondary analyses when including all lesions was no different compared to the primary analysis.

7.3. Discussion

The work demonstrated that for all lesions in our sample (both homogenous and heterogeneous), the Gleason grade hotspot is concordant with the volume hotspot in over 9 in 10 of all lesions.

We also found that in biopsy-naïve men, about 1 in 5 lesions are heterogeneous in grade. For these lesions, the Gleason grade and volume hotspot are discordant in about 2 in 10 lesions with approximately 10mm distance between the two.

7.3.1. Limitations:

There are a few limitations with this work to address. First, although this is a computer reconstruction based on precise 3-D pathology, a degree of error is inevitable. During clustering lesions, it is possible that some very small lesions might have been missed. To minimise the error, we used two methods for determining whether positive biopsies belonged to one specific lesion or not; which showed minimal variation in our findings.

Second, these findings may be valid in a biopsy-naïve population with suspicion of early prostate cancer and a PSA less than 15ng/ml. It is

likely, and previously shown that greater heterogeneity is present in more advanced disease ^{137,138}.

7.3.2. Clinical implications

Prostate cancer exhibits significant heterogeneity and the course of the disease appears defined by the dominant Gleason pattern hence tissue diagnosis remains key ¹³⁹.

Image guided biopsies are now heavily discussed in literature and appear to be the next step forward to complement the MRI based pathway. This work aimed to provide information to support further research into best-targeted biopsy practice for the best possible risk stratification for patients.

8. Chapter 8: Multivariate analysis of predictive factors for the presence of clinically significant disease

There are several risk score calculators for the detection of clinically significant prostate cancer, which utilise clinical data such as age, PSA, Digital Rectal Examination (DRE), ethnicity and family history. Additional information provided by MP-MRI may add to the prognostic value for the detection of clinically significant cancer and may substantially improve diagnostic accuracy.

Currently, risk calculators have been based upon either TRUS biopsy or prostatectomy data. As discussed previously, the inaccuracies of introduced by TRUS and the selection bias inherent to prostatectomy, presents significant limitations.

PROMIS is based upon 5mm Template Prostate Mapping, which is regarded as the gold standard for reliable detection of prostate cancer without the selection bias of prostatectomy. PROMIS collected detailed clinical information on all patients providing a unique opportunity to address several questions.

Aims and objectives

- Investigate which baseline factors are associated with presence of clinically significant cancer and determine whether MP-MRI adds substantially to the prognostic accuracy beyond using clinical data alone.
- Use PROMIS data to validate the diagnostic accuracy of the main currently available risk score calculators.
- Develop a risk score calculator using PROMIS data and validate it externally.

8.1. Summary of currently available risk score calculators

A recent systematic review of the literature for risk prediction models for presence of any cancer identified 127 calculators¹⁴⁰ yet, only 6 calculators met the inclusion criteria for their meta-analysis: included at least 2 model factors, included PSA, had been validated in at least 5 independent datasets and reported AUC values with 95% CIs.

These 6 scores are detailed below:

- ProstaClass: PSA, DRE, age, free/total PSA, prostate volume (from TRUS)
- Finne: PSA, DRE, free/total PSA, prostate volume (from TRUS)
- Karakiewicz: PSA, DRE, age, free/total PSA
- PCPT: PSA, DRE, age, ethnicity, family history, No. previous negative biopsies
- Chun: PSA, age, free/total PSA, sampling density (from TRUS)
- ERSPC: PSA, DRE, TRUS, prostate volume (from TRUS)

8.2. The PROMIS dataset

As discussed, PROMIS has MP-MRI and TPM data on 576 men in whom 230 were classified as having clinically significant prostate cancer on TPM using the primary definition for clinically significant cancer, which is defined as:

- Dominant Gleason pattern ≥ 4 and/or
- Any Gleason pattern ≥ 5 and/or
- Cancer core length ≥ 6 mm

Among other parameters, PROMIS collected baseline clinical data for: Age, PSA, family history, ethnicity, BMI (limited data).

In addition, the following parameters were acquired from the MRI reports: Gland volume (continuous data)

PSA density (PSA/MRI measured gland volume)
MRI score (ordinal data classified into 1, 2, 3, 4 or 5).

There were a total of 230 cases of clinically significant cancer in our PROMIS dataset of 576 men. Using the rule of thumb that there should be 10 cases per factor tested, we were well placed to investigate all the baseline data we have for PROMIS.

8.3. Statistical methods

Summary statistics

The distribution of any continuous variables will be checked for approximate normality or evidence of strong skewness. Regression models require that the residuals are normally distributed and highly skewed variables can lead to violations of this assumption.

Frequencies for the categorical variables will be assessed to decide whether groups should be combined. Ethnicity is the only variable where this could be a problem.

Model

Logistic regression modelling will be used to investigate each of the available factors for association with clinically significant cancer on TPM.

A 4-step approach was used:

STEP 1: a uni-variate model will test each factor alone.

STEP 2: a multi-variate model that includes all the clinical variables that demonstrated uni-variate p-values of <0.1 .

STEP 3: a multi-variate model that includes all the clinical variables that demonstrated STEP 2 p-values of <0.1 and all the MRI-based variables.

STEP 4: A final model will be confirmed that includes all factors with significant multi-variate p-values of <0.1 from STEP 3.

8.4. Sensitivity analyses

A non-linear effect of age will be investigated by adding an additional age-squared term into the model from STEP 3.

Characteristic [Number of men with missing covariate]	Men with clinically significant cancer N=230	Men without clinically significant cancer N=346	STEP 1 Odds ratio [95% CI] , p-value from univariate logistic regression model	STEP 2 Odds ratio [95% CI], p-value from multivariate clinical regression model*	STEP 3 Odds ratio [95% CI], p-value from multivariate clinical + MRI regression model*
CLINICAL DATA					
Mean (SD) age, years [0]	65.1 (7.4)	62.2 (7.5)	1.05 [1.03-1.08], <0.001	1.04 [1.01-1.07], 0.007	1.04 [1.01-1.08], 0.013
Mean (SD) PSA, ng/ml [0]	8.0 (3.0)	6.5 (2.7)	1.20 [1.13-1.28], <0.001	1.17 [1.09-1.25], <0.001	0.83 [0.67-1.06], 0.135

Mean (SD) BMI, Kg/m ² [62]	28.6 (4.3)	27.3 (4.5)	1.07 [1.03- 1.12], 0.001	1.08 [1.03- 1.12], 0.001	1.10 [1.05- 1.16], <0.001
<u>Family history of prostate cancer, n (%) [7]</u> No Yes	185 (81) 42 (19)	257 (75) 85 (25)	Reference 0.69 [0.45- 1.04], 0.076	Reference 0.82 [0.51- 1.33], 0.424	Referenc e 0.83 [0.46- 1.48], 0.526
<u>Ethnicity, n (%) [1]</u> White Black or Black British Other	202 (88) 16 (7) 12 (5)	300 (87) 23 (7) 22 (6)	Reference 1.03 [0.53- 2.00], 0.923 0.81 [0.39- 1.67], 0.569	N/A	N/A
MRI- DATA					
<u>MP-MRI score, n (%) [0]</u> 1 = Highly likely benign 2 = Likely benign 3 = Equivocal 4 = Likely	1 (<1) 16 (7) 34 (15) 70 (30) 109 (47)	22 (6) 119 (34) 129 (37) 50 (15) 26 (8)	Reference 3.0 [0.37- 23.5], 0.305 5.8 [0.8- 44.6], 0.091 30.8 [4.0- 236.1], 0.001 92.2 [11.9- 715.8],	N/A	Referenc e 2.91 [0.35- 24.0], 0.320 4.21 [0.53- 33.4], 0.174

malignant 5 = Highly likely malignant			<0.001		18.7 [2.36- 148.5], 0.006 36.7 [4.49- 300.0], 0.001
Mean (SD) prostate volume from MP- MRI scan, cc [0]	40 (16)	53 (21)	0.96 [0.95- 0.97], <0.001	N/A	1.00 [0.97- 1.03], 0.954
Median [IQR] PSA density, ng/ml per cc [0] #	0.21 [0.15- 0.29]	0.12 [0.09- 0.16]	6.5 [4.4- 9.6], <0.001	N/A	6.57 [1.37- 31.5], 0.019

* STEP 2 multi-variate model includes all clinical STEP1 variables with p-values <0.1. STEP 3 multi-variate model includes all STEP 2 and STEP 1 covariates with p-values <0.1

included in logistic regression models log transformed due to skewness

Table 8.1: Logistic regression analysis of prognostic factors associated with presence of clinically significant prostate cancer on TPM biopsy

Test result	Men with clinically significant cancer N=230	Men without clinically significant cancer N=346	Odds ratio [95% CI] , p-value, z-statistic from univariate logistic regression model
TRUS			
Definition 1 = negative	119 (52)	333 (96)	Reference
Definition 1 = positive	111 (48)	13 (4)	23.9 [13.0-44.0], <0.001, 10.2
MP-MRI DATA			
MP-MRI score = 1 or 2	17 (7)	141 (41)	Reference
MP-MRI score = 3, 4 or 5	213 (93)	205 (59)	8.6 [5.0-14.8], <0.001, 7.84

Table 8.2: Logistic regression analysis of binary MP-MRI and TRUS for presence of clinically significant prostate cancer on TPM biopsy

Characteristic	Odds ratio [95% CI], p-value, z-statistic
CLINICAL DATA	
Age, years	1.04 [1.00-1.07], 0.037, 2.09
BMI, Kg/m ²	1.13 [1.07-1.19], <0.001, 4.21
MRI-BASED DATA	
MP-MRI score = 1	Reference
MP-MRI score = 2	1.95 [0.23-16.3], 0.537, 0.62
MP-MRI score = 3	2.89 [0.36-23.3], 0.319, 1.00
MP-MRI score = 4	10.54 [1.31-84.79], 0.027, 2.22
MP-MRI score = 5	18.78 [2.27-155.34], 0.007, 2.72
Log PSA density, ng/ml per cc	2.81 [1.63-4.84], <0.001, 3.74
TRUS DATA	
Definition 1 = negative	Reference
Definition 1 = positive	17.08 [8.23-35.39], <0.001, 7.63

Table 8.3: Final model from multivariate logistic regression analysis of significant factors associated with presence of clinically significant prostate cancer on TPM biopsy

Characteristic	Odds ratio [95% CI], p-value, z-statistic
CLINICAL DATA	
Mean (SD) age, years	1.05 [1.02-1.09], 0.003, 2.99
Mean (SD) BMI, Kg/m ²	1.14 [1.08-1.20], <0.001, 4.78
MRI-BASED DATA	
MP-MRI score = 1 or 2	Reference
MP-MRI score = 3, 4 or 5	3.78 [1.92-7.44], <0.001, 3.85
Log PSA density, ng/ml per cc	4.04 [2.45-6.68], <0.001, 5.45
TRUS DATA	
Definition 1 = negative	Reference
Definition 1 = positive	21.5 [10.54-44.06], <0.001, 8.41

A sensitivity analysis including age as a squared variable did not indicate any statistical significance in the final model.

Table 8.4: Model from multivariate logistic regression analysis of significant factors (including MRI as a binary variable) associated with presence of clinically significant prostate cancer on TPM biopsy

Characteristic Bonferroni	ROC				
	Area	Std. Err	Chi2	df	Pr>chi2
TRUS alone (standard	0.7284	0.0185			
Binary MRI alone	0.6600	0.0167	7.9447	1	0.0048
0.0289					
MRI 1-5 alone	0.8124	0.0190	11.0267	1	0.0009
0.0054					
Table 3 with TRUS	0.9067	0.0138	111.0314	1	0.0000
0.0000					
Table 3 without TRUS	0.8512	0.0177	24.362	1	0.0000
0.0000					
Table 4 with TRUS	0.8913	0.0147	98.5172	1	0.0000
0.0000					
Table 4 without TRUS	0.8126	0.0194	9.9729	1	0.0016
0.0095					
<i>Note: 62 observations ignored because of missing values.</i>					

Table 8.5: ROC analysis (against TPM) for TRUS-biopsy (standard), MRI (binary or 1-5 scale) and linear predictors from models in Tables 3 and 4 including and excluding TRUS-biopsy. Optimal model highlighted in red. The Bonferroni adjusted p-values compare each ROC area with TRUS alone (standard)

8.5. Conclusion:

From the above analyses we can conclude:

- TRUS-biopsy alone and a binary MRI score alone perform significantly worse than models 3 and 4.
- In isolation, using MRI as a scale of 1-5 provides a much improved AUC than using it as a binary variable alone (0.81 vs 0.66)
- The model in Table 3 represents the optimal model for prediction. Without TRUS, the AUC drops from 0.91 to 0.85. However, as the pathway involves attempting to predict which men should and should not proceed to biopsy, this is less relevant.
- When comparing models 3 and 4, use of MRI as a scale of 1-5 does not add much over using the binary cut off at 3.
- The addition of TRUS-biopsy data improves the AUC markedly for both Models 3 and 4 and might justify the role of biopsy in those cases where uncertainty exists.

9. **Chapter 9: Methodological considerations in PROMIS**

PROMIS set out to provide level 1_b⁹⁶ evidence on the diagnostic accuracy of an MP-MRI dependent pathway in diagnosis of gland confined prostate cancer with MP-MRI used in a triage capacity⁴⁴. In order to do so, PROMIS had to first avoid the shortcomings seen in past and ongoing research as detailed in (*Chapter 2*). Second, it had to fill the knowledge and evidence gap on several key issues regarding wide scale implementation of the pathway (*Chapter 2*) and finally, provide enough data to support future research into implementation of the proposed pathway. Many of these issues are summed up in the following section.

9.1. **Strengths**

9.1.1. **Robust trial design and conduct:**

9.1.1.1. ***The use of a validating paired cohort design***

A validating paired cohort design was chosen for PROMIS as not only does it provides level 1_b⁹⁶ evidence on diagnostic accuracy/validity (sensitivity, specificity, positive and negative predictive values), the ability to assess the same pathology and disease burden with all 3 tests lends itself perfectly to prostate cancer where its different histological patterns, multi-focality and (prior to PROMIS) irreproducible sampling due to TRUS-biopsy as detailed in (*Chapters 1 and 2*) presented significant challenges to different designs as for example, a randomized controlled trial⁴⁴.

9.1.1.2. STARD compliance, robust quality control and monitoring:

PROMIS was designed and conducted in accordance to the STARD⁹⁷ (Standards for Reporting of Diagnostic Accuracy) guidelines. To eliminate potential biases (Chapter 2), robust **blinding** of clinicians and patients to trial intervention results was implemented. Patients were only given the results after the conclusion of all trial interventions and all the results were available. Each clinician involved in the conduct of a trial intervention was given a pre-agreed set of clinical information, (PSA, age, other risk factors such as family history and ethnicity) and was otherwise blinded to the conduct and outcomes of all other interventions. For example, the pathologist reporting the TPM-biopsy of a patient was unaware of the results of the patient's TRUS biopsy and MP-MRI results, and vice versa.

This was further maintained by the use of a centralized reporting database held by the MRC CTU, where all reports were submitted directly and independently without the involvement of any other trial clinicians with the results only released back to the clinicians and patients once all the trial interventions had been completed. The database was supervised and monitored by both the TMG and the TSC in its DMC capacity. Only one patient was

accidentally unblinded and withdrawn across the whole recruited cohort.

Standardization of trial conduct was another priority for PROMIS across all trial interventions. All trial visits and interventions were conducted using strict standardized SOPs. Reporting was conducted on standardized CRFs (Case Report Forms), which are reviewed centrally for data return quality and monitored by the DMC.

To cater to such high standards of conduct, **centralized training** was arranged for all personnel involved in PROMIS whether in a clinical or a non-clinical capacity through training materials, sessions and site visits, both in general trial conduct and on the specific tasks assigned to each person. Prior to each site's start of recruitment, an induction site visit was undertaken to insure all protocols were in place and to support the site and answer all queries.

In regards to conduct of CPB, all contributing clinicians had experience with the conduct of TPM and TRUS biopsies and were supervised initially by an experienced clinician to ensure the SOP was followed accurately. Expert clinicians remained available for advice or further training as the need arose.

MP-MRIs were reported by dedicated urologic radiologists with previous prostate MRI reporting experience. Radiologists underwent centralized training involving an initial whole day course, in which 20–30 cases were reviewed individually, scored, and then reviewed as a group. A further training day occurred after the pilot phase with further 20–30 cases reviewed individually and collectively.

Quality control and assurance was maintained by continuously reviewing all CRFs and data returns from each center by the MRC and the DMC and highlighting any anomalies; site visits and access to experienced clinicians and expert trial data managers were arranged on demand or need.

MP-MRI quality control was seen as a priority for the success of PROMIS, other than the detailed training, SOPs and CRFs, all MRI scanners and imaging protocol setup were reviewed, verified and signed off prior to commencement of recruitment in each site.

Also each individual MP-MRI scan underwent quality control checks to ensure they were compliant with the ESUR guidelines⁹⁹. This was undertaken by an independent commercial imaging clinical research organization appointed through open tender (Ixico Ltd, London, UK).

9.1.2. Assessing a representative cohort accurately

PROMIS aimed to assess the triage role of MP-MRI in the population of men suspected of prostate cancer. To assure a representative sample was recruited, the ***inclusion criteria*** (Table 3.2) allowed almost all men suspected of cancer to enroll while excluding confounders, as the use of 5-alpha-reductase inhibitors, or recent urinary tract infections, which may affect the MP-MRI and biopsy results. Enrolling ***biopsy-naïve*** patients alone also serves that purpose and reflects the real clinical scenario of a patient early in the diagnostic pathway whilst removing any post-biopsy artifact impacting on the quality of MP-MRI.

Power calculations conducted prior to recruitment ensured a sample size large enough for PROMIS to report accurately on several assumptions of disease prevalence and thresholds of disease significance as detailed in (Section 3.9.7); something that was not performed in any study to date.

The use of an appropriate and accurate reference standard in the form of TPM-biopsy not only allowed accurate disease characterization, it also avoided the spectrum/selection biases associated with the other procedures (Section 2.4) by allowing most men suspected of prostate cancer to undergo both reference and standard tests in a CPB format.

9.1.3. Reflecting clinical practice and it's variability:

To assess the wide implementation of MP-MRI, PROMIS must be sensitive to the variations inherent with wide implementation. The ***multicentre design*** reflected practice in both expert tertiary academic hospitals centres and general district hospitals, serving different patient demographics and geographical areas within the UK. MRI scanners from ***different manufacturers*** were included although in reality this was only Siemens and Philips. Radiologists with ***variable degrees of prior experience*** were involved in the trial. PROMIS was the only trial to collect data that allowed assessment of these variables including ***inter and intra-observer variability*** of different reporters in interpretation of MP-MRI, the variation of patient demographics and cancer prevalence across geographical areas among others.

9.1.4. Collecting high quality validated data:

PROMIS was the only study available to date, that enjoyed such a unique validated cohort and it is not likely a similar large-scale trial will be conducted afterwards. PROMIS maximized the data return in order to provide material for future research and allowing the development of further ideas. The detailed sampling and reporting format used in histological reports (*section 3.9.4*), allows PROMIS to flexibly interrogate the data across different current and future ***definitions of disease significance*** to cater to the ongoing controversy on defining significant disease. MP-MRI CRFs collected additional information on

disease location within the prostate, the accuracy of independent imaging sequences among others, which are discussed in further detail in the upcoming sections. An additional optional translational arm (PROMIS-T) collected additional serum and urine samples for future collaborations. PROMIS patients will be followed through **NHS linkage** to provide data on long-term outcome of their diagnosis and management.

9.2. Limitations of PROMIS

As with any clinical trial, the PROMIS design came with some inherent limitations. These limitations are a result of compromises deemed necessary to fulfill the goals of the study.

First, conducting detailed, accurate 5mm TPM sampling as per SOP is limited by the size of the template grid equipment and interference of the bony pubic arch with needle insertion. This meant that men with very large prostates (>100ml) had to be excluded from the study as performing a full 5mm TPM was not feasible or will not be of the required accuracy for the gold standard. This factor may have actually had a detrimental impact on the high negative predictive value, a factor which is high reliant on prevalence, as a result of a decrease in the proportion of true negatives in the study population. This limitation was acceptable as TPM remained the best available option for accurate stratification and introduces significantly less biases compared to for

example radical prostatectomy. It is worth noting that from the 740 patients registered for PROMIS, 69 (9%) of patients were withdrawn due to prostate size. This produces a degree of selection in the PROMIS group that must be acknowledged yet it is offset by the fact that the men who were subsequently withdrawn from the study did not differ from those who completed it as detailed in (*section 4.1*).

Second, some systematic error may have been introduced into the standard test by the sequence in which TPM-biopsy and TRUS-biopsy were performed, and we were unable to control for this. Carrying out TPM-biopsy before TRUS-biopsy may have contributed to the poor accuracy of the standard test due to swelling, distortion and tissue disruption. The sequencing was based on patient safety considerations and on the need to preserve the integrity of the reference test.

Infection is a major risk associated with TRUS-biopsy due to breaching of the rectal mucosa. Participants might have been exposed to excess risk if bacteria had been introduced into the prostate prior to multiple needle deployments of an inherently sterile TPM-biopsy. However, we found no difference in the core lengths between TRUS biopsy and TPM-biopsy indicating that core quality at least was not affected.

Third, to maintain blinding, we did not target MR-suspicious lesions and cannot accurately assess clinical utility of a MR-targeted biopsy approach. This was to maintain the integrity of our diagnostic assessment of MP-MRI, which is the main purpose of PROMIS.

Finally, PROMIS was conceived and designed several years before its conclusion. The design ambitiously attempted to maximize the benefits and collect as much high quality data as possible on multiple facets of the topic examined. Yet since recruitment started, the atmosphere in the NHS has rapidly changed with significantly increased pressures on already limited clinical resources. We were soon to realize during the pilot phase that the PROMIS procedures are too time and resource consuming for the current state of the NHS, and if we continued as originally planned we ran a significant risk of not completing recruitment on time. To avoid this we implemented several simplifications to our SOP, which allowed us to adapt to the resource constraints without sacrificing our goals and overall determination of accuracy when we moved forward with the main phase of the trial as detailed in (*Section 3.9.4*).

Although we included some measurement of inter-observer variability, these were between two expert readers. Due to time and resource constraints we were not able to report on variability across radiologists with different levels of experience or across different MRI manufacturers as we initially set out to do. This is mitigated by the fact that the results between the main site (UCLH) and all other sites were almost identical as detailed in (*section 6.1*). Further work is required to measure these variables and is planned in our future work. Related to this issue was our use of the LIKERT scale of MP-MRI reporting. We

chose this as this was the system available at the time and subsequent studies have shown no significant differences between LIKERT and PIRADS, with some showing that LIKERT might perform better in the transition zone. In order to resolve this issue, further work will be required whereby radiologists are asked to report using both systems by having scans assigned to them in random order and the same scans assigned to them at a later date without identifiers for reporting by another reporting system.

10. Chapter 10: Discussion of the PROMIS results

PROMIS is the first study to present blinded data on the diagnostic accuracy of both MP-MRI and TRUS biopsy against an accurate reference test in biopsy-naïve men with a suspicion of prostate cancer. It is also the largest registered trial to date in this at-risk population. PROMIS represents level 1b evidence for assessment of diagnostic accuracy. Its design allowed highly reliable and precise accuracy estimates for both TRUS-biopsy and MP-MRI across a number of centers, and the conduct and reporting of each test was standardized and performed blind to the other test results.

10.1. Generalizability and cancer prevalence

In terms of generalizability, the PROMIS patient set is representative of the general population in the UK. When examining the withdrawals, there were no significant differences between those who withdrew after registration and those who completed all tests as discussed in *section (4.1)*. We would expect this to be the case as the MP-MRI findings were blinded to patients and physicians. The men with large prostates who were withdrawn after consent may have reduced the number of men with no cancer or clinically insignificant cancers, as larger prostates tend to lead to elevated PSA due to benign prostatic hyperplasia as discussed previously.

Whilst a significant number of men were screened in order to recruit our cohort, the screening log data indicated no differences in age or PSA between patients who were screened as eligible for the study but who did not enter the study, and those who did enter the study as detailed in *section (4.1)*.

The prevalence of any cancer or clinically significant cancer was much higher than we anticipated (*Section 4.7*). This was a function of the

combined biopsy strategy – a diagnostic approach that has rarely been tried before. The effect was to identify a large, and almost certainly representative sample of men with prostate cancer from the cohort referred for biopsy. This figure might have also been influenced by our withdrawal of large prostates (>100cc) which could not be biopsied using the reference test and were more likely to test negative or non clinically significant

Nonetheless, our data is not an outlier with respect to the literature. Previous TPM-biopsy studies have found a higher prevalence of clinically significant prostate cancer than studies that used TRUS-guided biopsy¹⁴¹⁻¹⁴³. No single sampling system identifies all disease¹⁴⁴ hence the combination of TRUS-guided biopsy and TPM-biopsy probably represents the best detection strategy that we have available.

The degree to which the prevalence of clinically significant prostate cancer is contingent on the sampling method used does raise questions about where the threshold of clinical significance should be placed. This highlights the uncertainty around what constitutes clinical significance in prostate cancer¹⁴².

PROMIS was conducted within a healthcare system that does not have a formal prostate cancer-screening program in place. In jurisdictions where screening has been in place for some time it is likely that the prevalence of clinically significant cancer among men undergoing biopsy will be lower compared to the UK, where a formal population-based PSA screening program is not recommended.

10.2. PROMIS in light of current literature

Our results fell within the expected ranges reported on the current published data and recent systematic reviews discussed in (*Chapter 2*) where we detailed the methodological shortcomings of these studies

which resulted in a wide range of values on systematic reviews which solidifies the current understanding of the value of MP-MRI and positively reveals the shortcomings of the technology in order to understand its best utilisation as discussed in this and the following chapters.

10.3. Impact of MP-MRI on the current pathway

On TPM-biopsy, 408 (71%) of men tested positive for any cancer, of which 230 (40%) cases were clinically significant according to the primary definition of clinical significance (Gleason $\geq 4+3$ of any length and/or a maximum cancer core length of ≥ 6 mm of any grade in any location on TPM-biopsy). A MP-MRI score of 3 or above was designated as a suspicious scan.

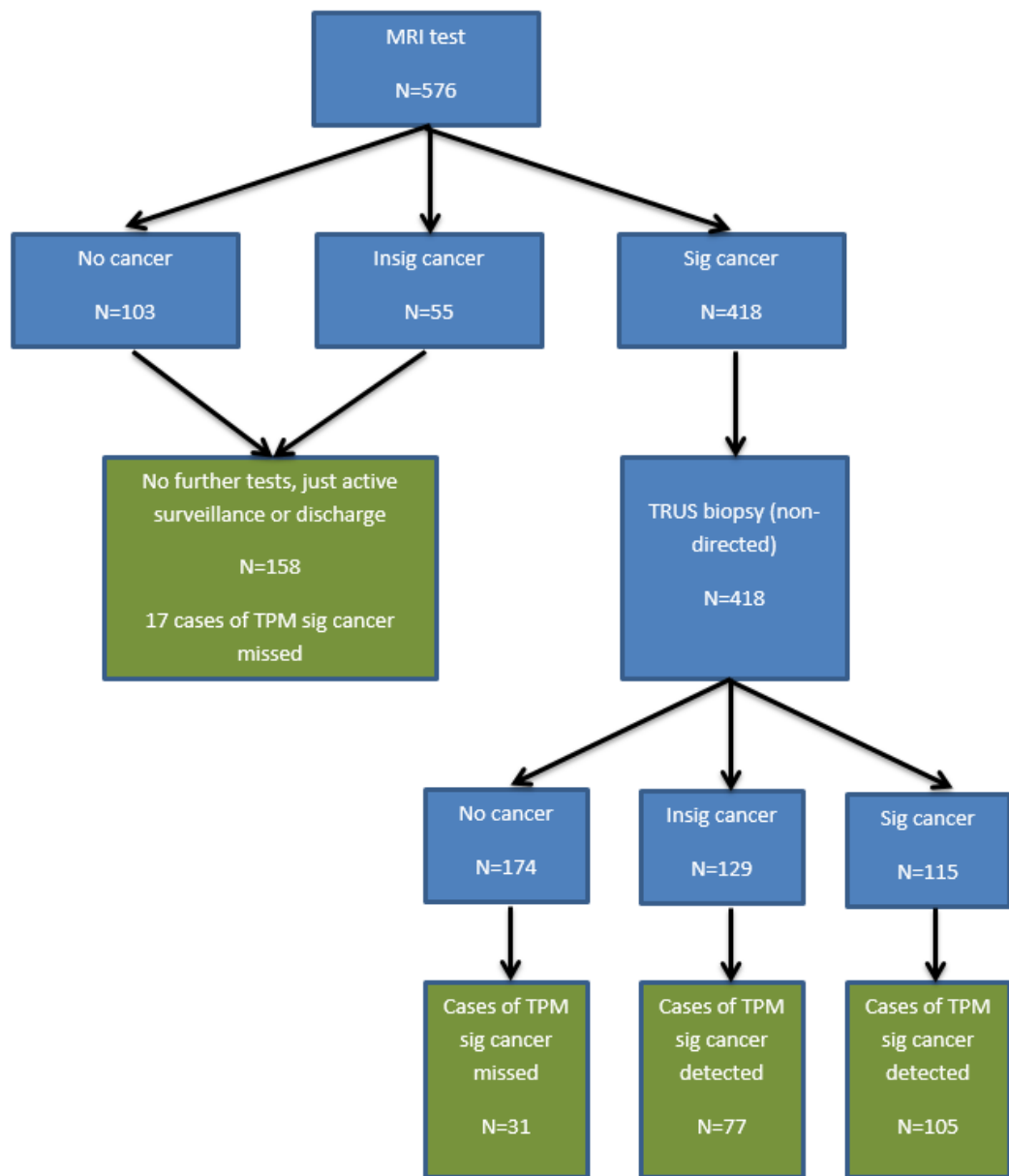
MP-MRI was more sensitive 93%[95%CI 88-96] than TRUS-biopsy 48%[42-55], ($p < 0.0001$) and less specific 41%[36-46] versus 96%[94-98], ($p < 0.0001$). Further, using these primary definitions and thresholds the negative predictive value of MP-MRI was 89% and the positive predictive value was 51% as discussed in detail in *Chapters (IV and V)*.

To assess the impact of introduction of MP-MRI to the current diagnostic pathway, we compared the standard of care, where all men undergo a TRUS biopsy to 2 postulated scenarios of implementation where only men with a suspicious MP-MRI (Likert score ≥ 3) would go on to biopsy and the remainder would receive active surveillance or would be discharged as detailed in *table (8.1)*.

10.3.1. Worst case scenario

Under the worst-case scenario, a standard TRUS-biopsy would be performed but MP-MRI would not be used to direct needle deployment. The TRUS-biopsy results for each patient have

been used to calculate over-diagnosis as described in (Figure 10.1) and Table (8.1)



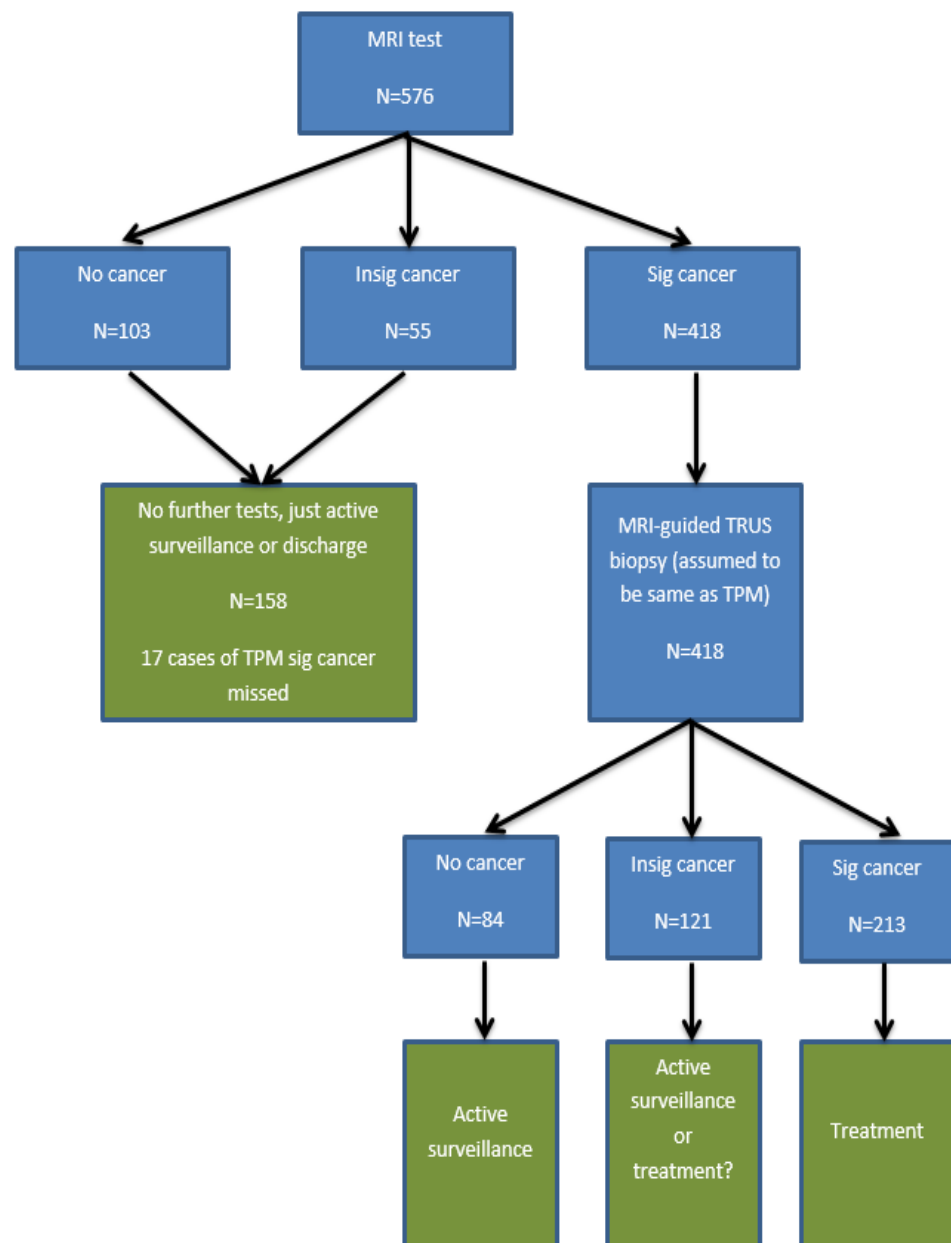
(Figure 10.1): Flow chart showing worst-case scenario (TRUS-biopsy directed by MP-MRI)

- Number of biopsies = 418 (73% of total)
- Significant cancer detected = 77+105=182 (32% of total), (79% of 230 with TPM sig disease)
- Significant cancer missed = 17+31=48 (8% of total), (21% of 230 with TPM sig disease)

- Over-diagnosis = $244 - 182 = 62$ (11% of total), (18% of 346 without TPM sig disease)

10.3.2. **Best case scenario:**

Under the best-case scenario, the TRUS-biopsy needle deployment would be guided by the MP-MRI findings, and the results presented assume that such targeted biopsies would achieve similar diagnostic accuracy as TPM-biopsy^{145,146}.



(Figure 10.2): Flow chart showing best-case scenario (TRUS-biopsy directed by MP-MRI)

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- Number of biopsies = 418 (73% of total)
 - Significant cancer detected = 213 (37% of total), (93% of 230 with TPM significant disease)
 - Significant cancer missed = 17 (3% of total), (7% of 230 with TPM significant disease)
 - Over-diagnosis if insignificant cancers offered surveillance = 0

For both these scenarios, 158/576 men (27%) might avoid a primary biopsy, because they would have a non-suspicious MP-MRI with a low (1 in 10) probability of harboring significant cancer. For the worst-case scenario, an absolute reduction in the over-diagnosis of clinically insignificant cancers might be seen, of 28/576 (5%) fewer cases (relative reduction of 31% [95% CI 22-42%] compared with current standard. However, in this worst-case scenario important information on tumor location would not be used, with consequent lower numbers of clinically significant cancers missed compared to standard care.

Under the best-case scenario, over-diagnosis might be increased to 21%, i.e. there would be 31/576 (5%) more cases. However, this figure is based on the probability of detecting clinically insignificant cancers on TPM-biopsy and therefore an over-estimation. Nonetheless, if the MP-MRI information was used for biopsy deployment in this scenario, it might also lead to 102/576 (18%) more cases of clinically significant cancer being detected compared with the standard pathway of TRUS-biopsy for all. In practice, we envisage that the actual impact of including MP-MRI into the pathway would lie somewhere between the best- and worst-case scenarios.

	TRUS-biopsy alone pathway	MP-MRI followed by standard, non-directed TRUS biopsy (worst case scenario)	MP-MRI followed by MRI-directed TRUS-biopsy (best case scenario)
Primary biopsy	576 100% [99-100]	418 73% [69-76]	418 73% [69-76]
Over-diagnosis (insignificant cancer detected)	90 16% [13-19]	62 11% [8-14]	121 21% [18-25]
Significant cancer correctly detected	111 19% [16-23]	105 18% [15-22]	213 37% [33-41]
Under-diagnosis (significant cancer missed)	119	17+31+77	17

For all percentages, the denominator used is the total number of cases, n=576 with 95% confidence intervals provided in square brackets.

**(Table 10.1): clinical implications for the introduction of MP-MRI
as a triage test to the standard pathway**

11. Chapter 11: Towards implementing a MP-MRI pathway: Future research

PROMIS has clearly shown that a MP-MRI dependent pathway is significantly superior to the standard of care TRUS-biopsy pathway yet, it is not without disadvantages. The data from PROMIS advocates large-scale implementation and use of MP-MRI in clinical practice yet there remains several issues to address.

11.1. Determining the most suitable MRI parameters

As discussed in *section (3.9.1)*, The MRIs were reported in sequence, with T2-weighted images reported first, T2-weighted and diffusion-weighted images reported together, and then a third report issued for T2-weighted with diffusion and dynamic contrast enhanced (DCE) scans together. The reporting form is shown in (*Figure 3.2*).

This allows a unique opportunity to investigate the added diagnostic value of each sequence to decide on the most appropriate combination of MRI parameters to reach the best possible diagnostic accuracy. For example, DCE sequences value has always been in question and under the latest PIRADS V2.0 recommendations, it is ignored in assessment of peripheral zone cancer. DCE requires contrast (with its need for intravenous access, medical supervision and contrast-related risks) and an additional 10-15 minutes of scan time, it is useful to determine whether this additional resource and cost is justifiable by added diagnostic accuracy.

11.2. Management of the post MRI patients

Patients who have a positive MP-MRI (LIKERT score of 4 or more), a biopsy is clearly indicated. We have postulated different biopsy approaches in *Chapter 10* and an MRI guided or informed biopsy presents the most favorable approach yet so far, there is not agreed protocol or standard of operation in the conduct of this procedure. There is no agreed recommendation on whether a single biopsy core from the suspicious area is enough to accurately risk stratify the disease or whether multiple cores are needed especially with the heterogeneous nature of the disease and the presence of different Gleason scores within the same lesion. Also, should these biopsies target the geometric center or the longest axis of the lesion on the presumption that it harbors the highest risk disease or should we attempt to interrogate the whole lesion with several samples We have used the PROMIS pilot data to reconstruct 3D interpolated models of each lesion detected (*Chapter 8*)¹¹⁸. This showed that in majority of cases, targeting the longest axis reflects the most significant disease yet further research on the methods and techniques of targeting whether through visual fusion, MRI to ultrasound registration or in bore MRI guided targeting is most favorable. Issues with needle deflection and placement errors also still require significant research.

Patients with an equivocal MP-MRI (LIKERT score of 3) are a particularly important group. In PROMIS, 29% of patients received a

LIKERT score of 3 yet almost 80% of this group (22% of total) had no or insignificant disease on TPM with only 20% (6% of total) were proven to have significant disease which means a substantial amount of men will move on to biopsy. This is a significant burden to patients and will have negative cost implications to the pathway. Further research is required to improve diagnostic accuracy in this subset. A possible answer is to combine other parameters with the MRI results in making the decision to biopsy or not. The PROMIS data uniquely offers the opportunity to assess multiple factors as for example, PSA and PSA density, age, ethnicity and DRE findings and whether they can sway the biopsy decision. Our data on the multivariate logistic regression modeling demonstrates that PSA density might be a strong predictive factor. Recent evidence from other groups have shown the same that using PSA density of <0.15 or 0.12 can reduce the false negative rate for MP-MRI scores of 3 or less to 0-5%^{147,148}. The accurate reference standard also presents a unique opportunity to develop and test computer aided detection algorithms, which is part of our future research plans. Finally, one of the key issues is the ongoing controversy of an agreed threshold of disease significance. Should we accept a different threshold of significance, it is likely the number of equivocal MRIs will significantly change.

Patients with a negative MP-MRI (LIKERT score of 2 or less) still harbor insignificant disease and in a small subset misclassified significant disease. If these patients will avoid biopsy, there remain little

experience on MRI based follow up/surveillance protocols and whether or not, or how frequent they should be offered MRIs. Also, it is probable that some of these patients will over time harbor significant disease. It is logical to expect that this will be accompanied with changes on their MRIs but detailed research into when to trigger biopsies for this group of patients, whether due to MRI changes or to other parameters for instance PSA kinetics. In light of the above one must also wonder if it is possible to safely and confidently delay biopsies in patients with equivocal (LIKERT 3) MRIs until such changes are seen.

11.3. Large scale implementation

PROMIS tested MP-MRI across 11 centers of variable size, settings and experience. This has shown that MP-MRI can be implemented in different practice setting. Yet prior to a national roll out of such a pathway a few issues still require addressing.

11.3.1. Inter observer variability across different practice settings:

Despite the similarities in findings between the expert center and the participating site, PROMIS collected data to assess inter observer variability between different practice setting as smaller district hospitals where we expect most patients would present compared to expert centers. Similarly data has been collected to allow comparison between radiologists of different experience

and also scans performed on 1.5 T scanners from different vendors and makes.

Unfortunately due to time and funding constraints the analysis was not conducted as part of the initial work yet remains an essential part of future planned research.

11.3.2. Cost implications and service burden

With health economic analysis on the way, it remains clear that one of the main benefits expected from MP-MRI is to reduce the number of patients who undergo unnecessary biopsies safely which besides the important patient benefit, provides significant potential savings. PROMIS showed us that there is a significant number of patients who might undergo biopsies including the large cohort of patients whose MRIs receive a LIKERT score of 3/5 discussed above. Several options were discussed in *Chapter 11* to address this.

Similarly, the high prevalence of prostate cancer and the fact the MP-MRI is significantly less invasive than TRUS biopsy, we expect a sharp increase in referrals and the demand on MRI scanning time in hospitals will be significant.

Finally, MP-MRI of the prostate is still not a common clinical practice and most radiologists have little to no experience in

reporting it outside expert centers which may cause difficulty in coping with the demand expected.

To prepare for these issues, several steps are required. First, further improvements in the accuracy and interpretation of MRI as discussed. Second, the scanning process must be optimized to provide all the necessary data with the minimum scanning time. PROMIS collected data on the utility of each imaging sequence and we will be releasing a comparative analysis of the incremental utility of each in future. For example, should it be found that one of the parameters of MP-MRI, such as contrast enhancement, does not add significant information, the reduction of the scanning time and cost gained by omitting it may be very beneficial to counter the increased demand. Finally, robust training of radiologist will improve their accuracy and allow more radiologists the experience and knowledge to add prostate MP-MRI to their daily workload.

12. Conclusion

PROMIS has proven that MP-MRI carries a significant benefit to prostate patients that cannot be ignored. Especially with the current poor performance obtained from the standard of care TRUS biopsies, MP-MRI accurately risk stratifies a large proportion of men at risk of prostate cancer, especially when used to inform the subsequent biopsies.

MP-MRI has drawbacks. In a triage capacity, MP-MRI avoided biopsy in up to 27% of men who do not have clinically significant disease yet it would miss clinically significant cancer in 11% of this group and 3% of the overall cohort.

With the current data, MP-MRI should be employed nationally yet a recognition of further work needed to improve its performance and anticipate its drawbacks.

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14. Appendices

14.1. Appendix I

14.1.1. The PROMIS group

Trial sponsor:

University College London (UCL)

Trial coordination:

Medical Research Council Clinical Trial
Unit (MRC CTU) at UCL

Funders:

National Institute for Health Research
(NIHR) Health Technology Assessment
(HTA) & Prostate Cancer UK

Trial Management Group:

Professor Mark Emberton (Chief Investigator)
UCLH (Urologist)

Mr. Hashim Ahmed (Co-chief Investigator)
UCLH (Urologist)

Dr Ahmed El-Shater Bosaily
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Dr Alex Kirkham
UCLH (Radiologist)

Dr Alex Freeman
UCLH (Pathologist)

Dr Charles Jameson
UCLH (Pathologist)

Mr Richard Hindley
Basingstoke (Urologist)

Dr Christopher Parker
Royal Marsden (Translational Research)

Professor Colin Cooper
Royal Marsden (Translational Research)

Robert Oldroyd
Patient representative

Professor Richard Kaplan
MRC CTU (Program Lead/Oncologist)

Dr Louise Brown
MRC CTU (Project Lead/statistician)

Dr Rhian Gabe
University of York (Statistician)

Dr Yolanda Collaco-Moraes
MRC CTU (Clinical Operations Manager)

Cybil Adusei, Katie Ward
MRC CTU (Trial Manager)

Sophie Stewart
Katie Thompson
Claire Mulrenan,
Hannah Gardner

MRC CTU (Data Managers)

Carlos Diaz-Montana
MRC CTU (Data programmer)

Dr Chris Coyle
MRC CTU (Clinical Fellow)

Professor Mark Sculpher
University of York (Health Economics)

Dr Rita Faria
University of York (Health Economics)

Trial Steering Committee (also act as Data Monitoring Committee):

Dr David Guthrie (Chair)
Derbyshire Royal Infirmary (Oncologist)

Professor John Chester
University of Cardiff (Oncologist)

Professor Richard Cowan
Christie Hospital Manchester (Oncologist)

14.1.2. PROMIS trial protocol & appendices



University College London Hospitals 
NHS Foundation Trust



Developed with the
NCRI Prostate Clinical
Studies Group


**National Institute for
Health Research**

Part of the NIHR
National Cancer
Research Network
Portfolio

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

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

Protocol Version 4.0
06th September 2013

Authorised by:
Name

Professor Mark Emberton

Signature:



Role

Chief Investigator

Date: 6th September 2013

Name

Dr Louise Brown

Signature:

Role

Project Lead, MRC CTU

Date: 6th September 2013

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 at UCL (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.

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APPENDICES

Please refer to the most recent version of the 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
RN	Research Nurse
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 trans rectal 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 harboring 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.

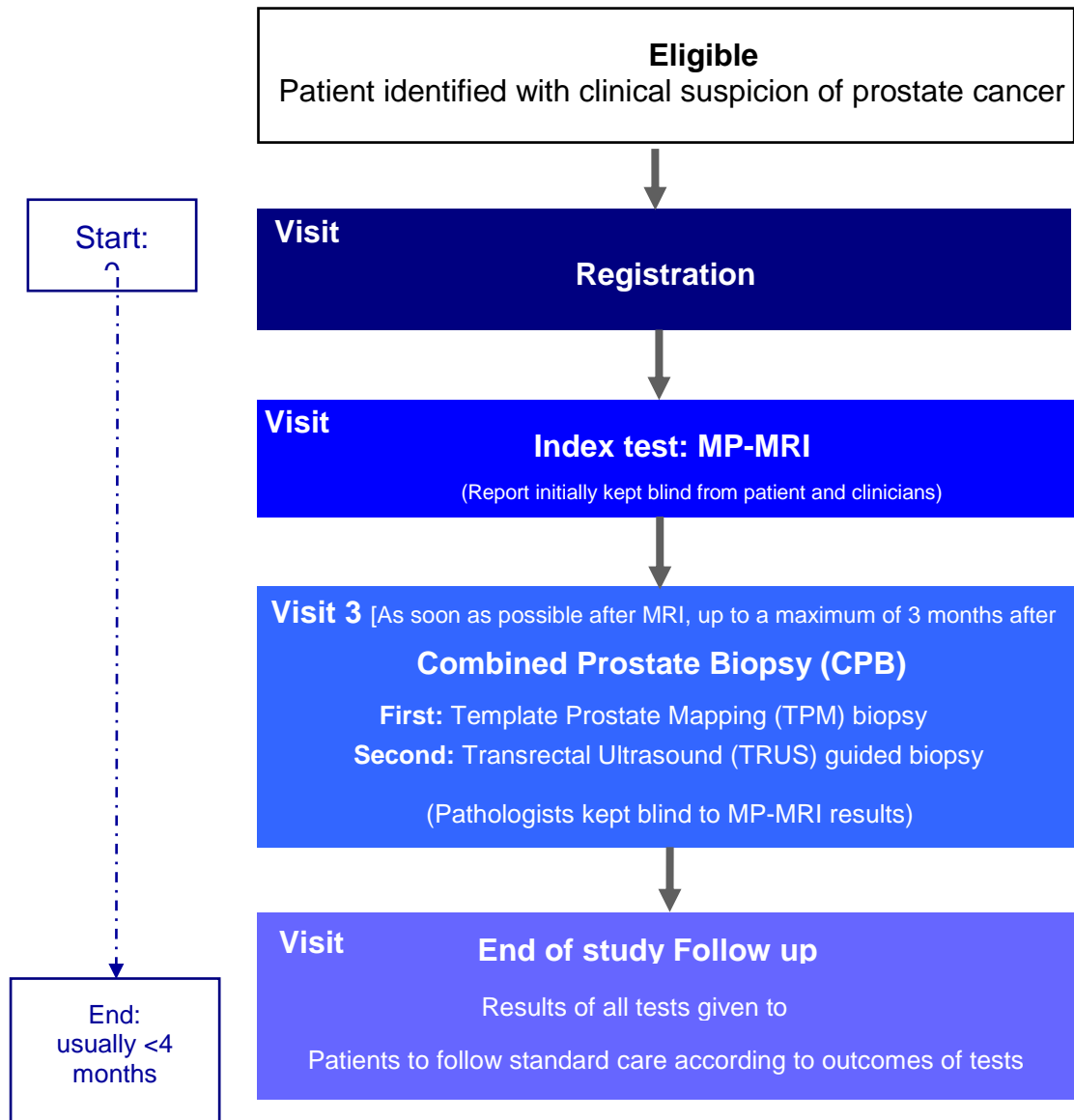
The study is divided into a pilot and a main phase. The pilot was run in two centres, University College London Hospitals NHS Foundation Trust and North Hampshire Hospitals NHS Trust and recruited 50 patients over one year. The pilot assessed recruitment and the safety of administering the tests, particularly the combined prostate biopsy (CPB) procedure of TPM and TRUS under general/spinal anaesthesia. Continuation to the main phase was recommended by the Trial Steering Committee acting as an Independent Data Monitoring Committee (IDMC) after review of the pilot data.

The main phase will be extended to at least 6 centres in total (including the 2 pilot centres), recruiting up to 714 men to have all 3 tests over an additional 2 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 and trial methodology. There will also be a simple review of the assumptions on which the sample size calculations are based, particularly in relation to the correlation between MRI and TRUS. It is expected that the sample size calculations will only be amended in very extreme circumstances where the assumptions are grossly incorrect.

Main Trial

1. Proportion of men who could safely avoid biopsy as determined by specificity and negative predictive values

2. Introduction & Background

2.1 General overview and rationale

There are approximately 40,000 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

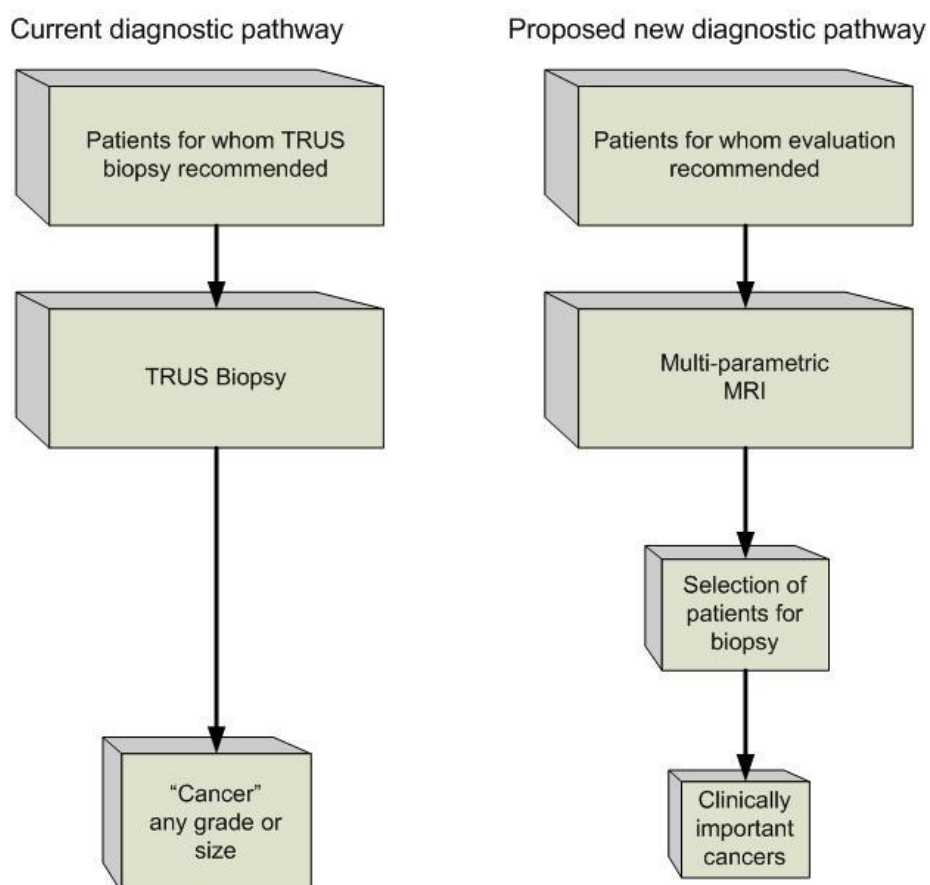
At present, a man is judged to be at risk of harbouring prostate cancer if he has any of the following: a raised serum PSA level (the majority), an abnormal digital rectal examination (DRE), a positive family history or a specific ethnic risk profile. Such men are currently advised to have a trans rectal 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



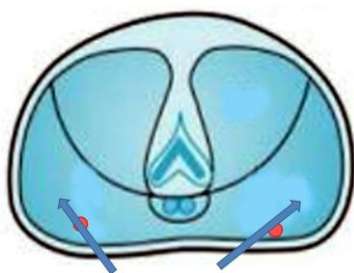
Please note: this is a proposed future diagnostic pathway and NOT the pathway patients will take in PROMIS (See Trial Schema 1.2)

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

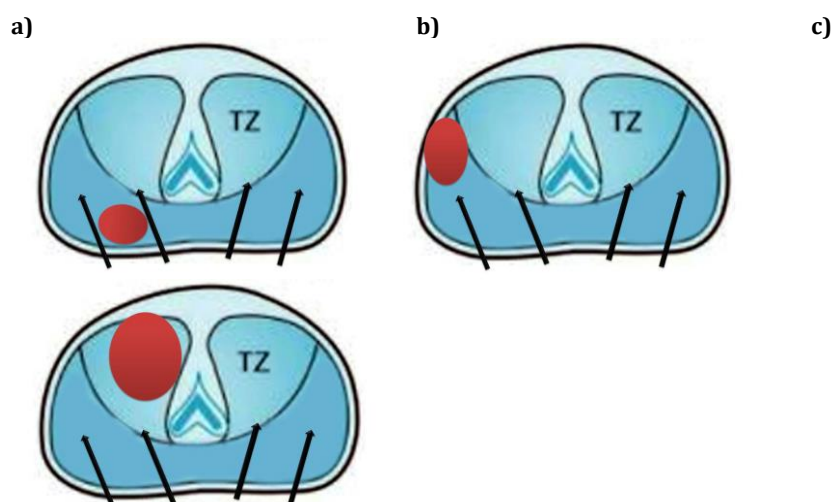
Figure 2: Over-detection of insignificant prostate cancer



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 trans rectal 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%), haemospermia (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

2.4.3	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-sampling³⁸ (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	AND/OR
	Cancer Core Length ≥ 6 mm	
<hr/>		
DEFINITION TWO:	Any Gleason pattern ≥ 4	AND/OR
	Cancer Core Length ≥ 4 mm	

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 had screened 339 men by the time the 50th patient attended their end of study visit in May 2013, thus creating the 50 patients included in the pilot analysis. They were recruited from two centres (University College London Hospitals (UCLH) NHS Foundation Trust and Basingstoke and North Hampshire NHS Foundation Trust) over approximately one year. This allowed us to:

- Prospectively record the rate of sepsis following the CPB procedure*.
- Monitor the recruitment rate.
- Provide an estimate of the prevalence in the scanned population of prostate cancer according to DEFINITION ONE and DEFINITION TWO.
- Provide an estimate of key outcome measures (sensitivity and specificity of MP-MRI compared to TPM, inter/intra-observer agreement of the MP-MRI).
- Determine whether the sample size calculations needed to be revised.
- Provide evidence, which, together with data from the literature, might facilitate a preliminary assessment of cost-effectiveness, which, in turn, might 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 has been reviewed by the TMG and the independent Trial Steering Committee (TSC). To date, it has not been deemed necessary, for safety reasons, for recruitment of the study to be suspended.

Continuation to the main phase was 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 years. There will be ongoing central safety monitoring and regular review for safety and data quality.

2.8 Translational research

The charity, Prostate Cancer UK, is funding additional blood and urine samples to be collected from patients who give consent to do so. The following translational objectives will also be investigated:

- 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 has been delegated authority to perform and read MP-MRI and conduct biopsy procedures.
- Copies of the most recent version of the patient information sheet (PIS), GP letter and consent form on local headed paper.
- Signed and dated site accreditation form.
- Completed normal ranges form for site.
- Procedure training log, with at least one person trained and signed off to conduct and read MP-MRI and at least one named investigator to conduct 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 \leq 15ng/ml within previous 3 months
3. Suspected stage \leq T2 on rectal examination (organ confined)
4. Fit for general/spinal anaesthesia
5. Fit to undergo all protocol procedures including a trans rectal 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 \leq 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 of the site if they wish to address any queries or concerns. It will be emphasised that where patients 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 (90 days) of consent. Results are required for registration. If this test has been done as part of standard care and within the 3 month (90 days) 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 (90 days) 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. If this test is not available at the site, it can be omitted.
- **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 \leq 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 already been completed within the 6 months (180 days) 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.

Patients must be given the PROMIS Patient Card that provides details of their involvement in PROMIS, the dates of their test procedures and the use of anti-biotics administered after the CPB.

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 Tesla scanner with the patient in the supine position. T2, DW and DCE scans will be acquired. The patient card must be updated with the date of MRI scan.

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 only on the MRI case report form (CRF) and sent only to the MRC CTU by the local site radiologist. Paper copies will be stored locally as paper CRFs that cannot be viewed by other investigators; these reports will not be accessible on any NHS computer system. Each 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 for the radiological score assigned to Definition 2 cancer on the MP-MRI CRF 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 sent to the MRC CTU as a pdf via e-mail. The local radiologist must store a copy of the report securely so that no one else has access to it. **These results must be kept blinded. Results must not be reported to the clinician performing TPM/TRUS biopsies or to any central or additional radiologists.** 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 grouped together in 20 zones referred to as modified Barzell zones.

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.

Any person involved in performing the CPB procedure will be blind to the MRI results. TRUS guided biopsies will be done in the lithotomy 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.

The patient card must be updated with the date of the CPB and the anti-biotic use prescribed.

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 IXICO, an independent commercial company who have collaborated regularly with UCL.

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 will be proctored for at least the first two 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

Whilst it would be preferable to implement a blinding system that prevents access to patient results, the hospital systems cannot be blocked completely and thus an element of trust is assumed. Local investigators are expected to and will honour their commitment to remain blind to all results, until release is authorised by the MRC CTU. If an investigator inadvertently obtains access to results which should have been blinded to them they must report this to the MRC CTU and their local investigators. They must be excluded from involvement with that patient until results are released officially.

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 knowledge of the MP-MRI report results 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 by the local radiologist who will be excluded from any involvement with the CPB. 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. The results can also be unblinded if on MP-MRI a patient is found to have a gland of $\geq 100\text{cc}$ as this extent of enlargement is likely to make the results of the TPM unreliable. 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/Data 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 was 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 trans rectal route.

Each sepsis case that occurred during the pilot phase was reviewed by the TMG and Trial Steering Committee (TSC). The TSC also reviewed safety (e.g. sepsis, urinary retention etc.) at completion of the internal pilot study. One recommendation of the TSC was that a SOP should be written for handling cases of urosepsis and that this SOP should be made easily available for reference at each site. Patients need to be provided with a Patient Card that gives details of their involvement in PROMIS, the dates of their test procedures and the use of anti-biotics administered after the CPB as well as weblink details for the sepsis SOP. Patients will be asked to carry this card and present it to any treating clinician if there is a suspicion of post-CPB sepsis. The SOP has been written and is available online at the PROMIS website. The patient card provides details for the weblink to this SOP.

For the pilot phase, it had been agreed that if 2 cases of sepsis occurred, the study may be temporarily stopped while the TSC reviewed the data. During the course of the pilot study, one case of sepsis occurred so stopping of the study was not required.

For the main phase, all sepsis cases will be reported to the TSC along with a crude percentage of the number of cases of sepsis divided by the number of CPBs completed. Should the point estimate for this crude percentage ever rise above 4%, the study will be temporarily stopped while the TSC review the data.

In addition to cases of sepsis, all SAEs will be reported to the TSC but crude percentages will only be reported if requested by the TSC. This is because the SAE in question may be specific to one of the study tests and thus the denominator may change according to the percentage required.

The TSC can make recommendations regarding modifications to the study design. For example, if a sepsis rate of 4% is observed 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

Each site is responsible for reporting SAEs to the MRC CTU who will report these to the TSC and to UCL who are the sponsor and take responsibility for accurate reporting of these. 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 the TSC and 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 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)
Haemospermia	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:

- results in death
- is life-threatening
- requires hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- consists of a congenital anomaly or birth defect
- 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 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 (relative to TPM) will also be reported in terms of sensitivity, specificity, NPV, and PPV as listed in the section below. The same DEFINITION ONE pathology criteria for clinically significant cancer as used for TPM will be used for TRUS. 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 (using the radiological score assigned for definition 2 on the MP-MRI form) 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 both 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, specificity 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. Following review of the pilot data, the TSC did not make any recommendation to alter the target sample size.

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 follow the STARD (STAndards for the Reporting of Diagnostic accuracy studies) practice.

9.3.1 Pilot study

Safety

The pilot study data has provided an estimate of the rate of sepsis (requiring hospitalisation) following the CPB procedure (as detailed in section 7.1). This was 2% [95% CI 0-11%].

Recruitment rate

The pilot study will also inform recruitment rate for the main study. The pilot met its objective of recruiting 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 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 radiological score for MP-MRI (assigned to definition 2 on the MP-MRI CRF) 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		Total
		+ve	-ve	
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 (radiological score ≥ 3 assigned to Definition 2 on the MP-MRI CRF) and TRUS biopsies (DEFINITION ONE) in the subset of men found to have clinically significant prostate cancer according to DEFINITION ONE on TPM. 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 analysis⁶⁰ 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 latest version of the UK Research Governance Framework.

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} The internal pilot demonstrated that most men require a catheter to be placed for a number of days whilst prostate swelling resolves.

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
3. The rectum is cleansed with anti-septic solution so the risk of infection may be lower than a TRUS biopsy alone

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, three copies will be kept with patient's hospital notes and the original 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. As of 1st August 2013, the MRC CTU transferred to become a University Unit within UCL. It is now called The MRC CTU at UCL.

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 the latest version of the UK Research Governance Framework guidelines, 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 and ISRCTN registration numbers that have 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

Third Amendment

The PROMIS protocol was amended in September 2013. The following changes were made:

- Version control and date
- PROMIS logo inserted
- Change of contact details
- Clarifications to pre-registration investigations
- Trial schema slightly amended
- Maximum time between MRI and CPB set to 3 months. MRI will need to be repeated if the patient was scanned over 3 months since biopsy.
- Information on the pilot phase and recommendations from the TSC
- Pilot study figures inserted and aspects of pilot results detailed
- Number of compulsory CPB procedures to be proctored changed from 6 to 2, but with the possibility to extend this if required.
- Various clarifications to information in the protocol
- Highlighted importance of biopsy occurring a maximum of three months after the MP-MRI
- Patients will be left in the lithotomy position for their TRUS biopsy
- Additional criteria for unblinding the MP-MRI report. If a patient has a gland of ≥ 100 cc they will be withdrawn after their MP-MRI.
- Sepsis rate requiring TSC recommendation changed to 4%

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.](#)

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.

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- 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’.

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Appendices

Please refer to PROMIS Protocol Appendices:



University College London Hospitals 
NHS Foundation Trust



Developed with the
NCRI Prostate Clinical
Studies Group


**National Institute for
Health Research**

Part of the NIHR
National Cancer
Research Network
Portfolio

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

ISRCTN: 16082556

MRC: PR11

UCL reference number: 11/0009

REC reference: 11/LO/0185

Protocol Appendices Version 4.0
6th September 2013

Authorised by:
Name

Prof Mark Emberton

Signature:



Role

Chief Investigator

Date: 6th September 2013

Name

Dr Louise Brown

Signature:

Role

Project Lead, CTU

Date: 6th September 2013

APPENDICES

APPENDIX I: MAIN TYPES OF MR IMAGES

APPENDIX II: TEMPLATE PROSTATE MAPPING PROTOCOL

APPENDIX III: HEALTH ECONOMICS: EQ-5D

APPENDIX IV: 27 REGIONS OF INTEREST OF PROSTATE

APPENDIX V: VARYING SAMPLE SIZE (N) ASSUMPTIONS AND IMPACT

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

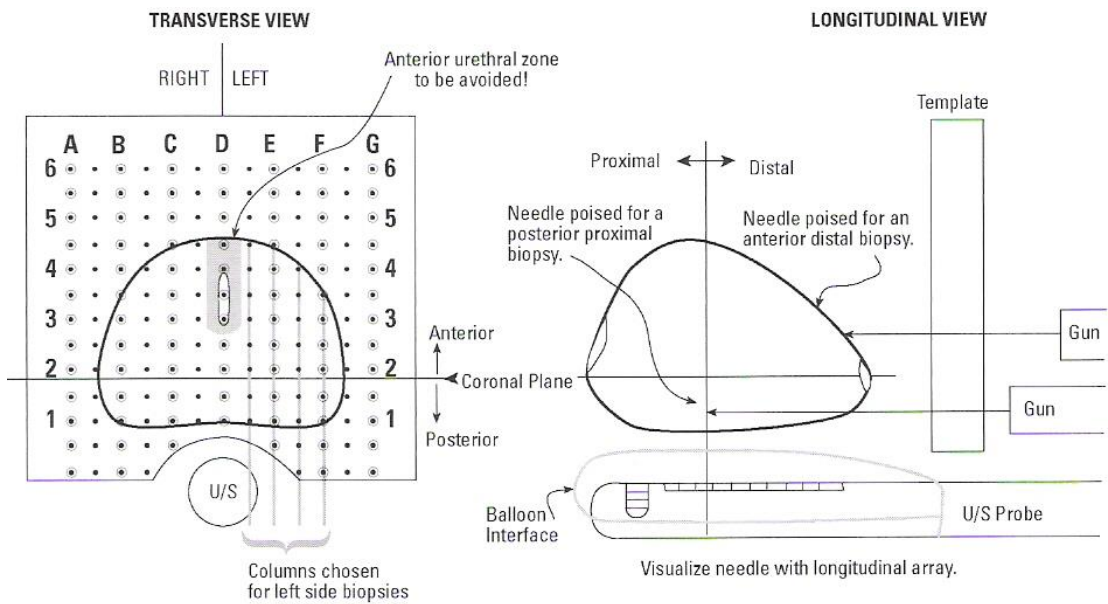
Dynamic Contrast Enhancement (DCE)

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 | <input type="checkbox"/> |
| I have some problems in walking about | <input type="checkbox"/> |
| I am confined to bed | <input type="checkbox"/> |

Self-Care

- | | |
|---|--------------------------|
| I have no problems with self-care | <input type="checkbox"/> |
| I have some problems washing or dressing myself | <input type="checkbox"/> |
| I am unable to wash or dress myself | <input type="checkbox"/> |

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

- | | |
|--|--------------------------|
| I have no problems with performing my usual activities | <input type="checkbox"/> |
| I have some problems with performing my usual activities | <input type="checkbox"/> |
| I am unable to perform my usual activities | <input type="checkbox"/> |

Pain/Discomfort

- | | |
|------------------------------------|--------------------------|
| I have no pain or discomfort | <input type="checkbox"/> |
| I have moderate pain or discomfort | <input type="checkbox"/> |
| I have extreme pain or discomfort | <input type="checkbox"/> |

Anxiety/Depression

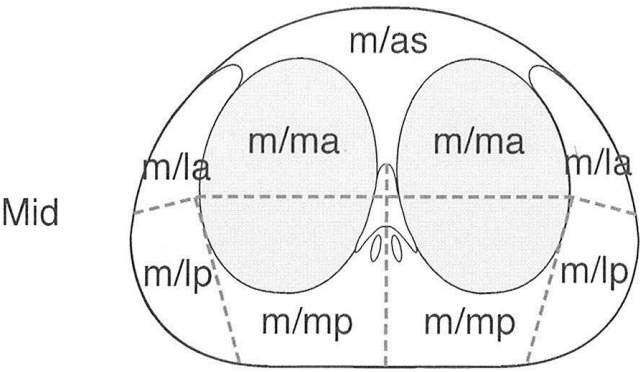
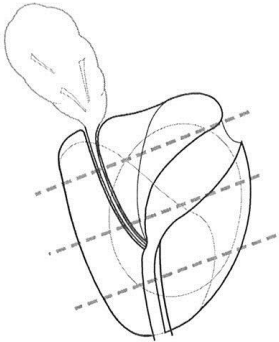
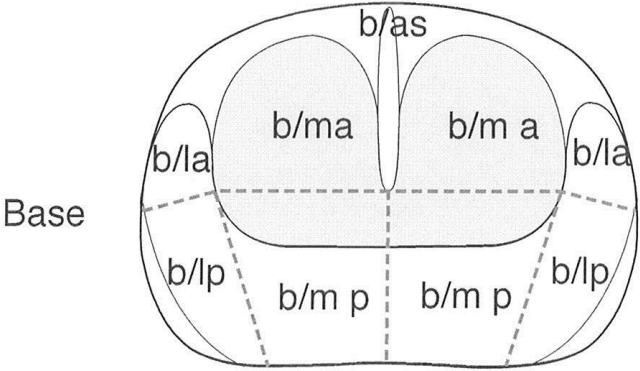
- | | |
|--------------------------------------|--------------------------|
| I am not anxious or depressed | <input type="checkbox"/> |
| I am moderately anxious or depressed | <input type="checkbox"/> |
| I am extremely anxious or depressed | <input type="checkbox"/> |

APPENDIX IV: 27 REGIONS OF INTEREST OF PROSTATE

Imaging - biopsy - pathology standardized report

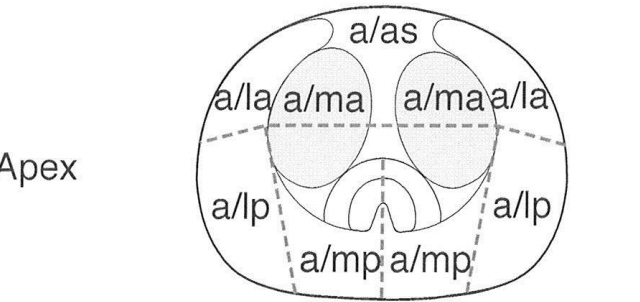
27 sectors scheme

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

Right

Left

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			Prevalence 15% DEFINITION ONE	Prevalence 25% DEFINITION TWO
MF-MRI results	Negative	Positive	Negative	Positive			
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.

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14.1.3. Patient information sheet

Version 4.0 6th September 2013

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

PROMIS: Prostate MRI Imaging Study

**An evaluation of multi-parametric magnetic resonance imaging in
the diagnosis and characterisation of prostate cancer**

ISRCTN 16082556

MRC: PR11

UCL reference number: 11/0009

REC reference: 11/LO/0185

We are inviting you to take part in this study because your doctors are considering you for a prostate biopsy. Doctors usually recommend a prostate biopsy if you have a high or rising Prostate Specific Antigen (PSA) level in the blood, or if your doctor can feel a lump in your prostate.

Before you decide whether or not to take part in this study, it is important for you to understand why the study is being done and what it will involve. Please take time to read the following information carefully. Talk with your GP, family or other people about the study if you wish.

PART 1 tells you the purpose of this study and what will happen if you choose to take part

PART 2 gives you more detailed information about the conduct of the study

Please ask us if there is anything that is not clear or if you would like more information, you can have as much time as you need to consider the study, but you will have **at least** 24 hours to decide whether you want to take part.

PART 1

1. What is the purpose of the study?

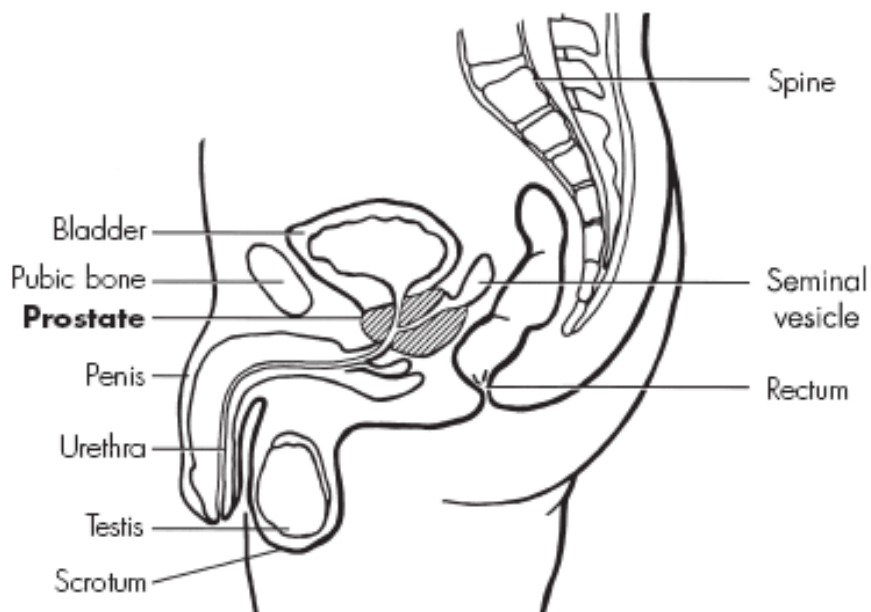
The purpose of this study is to test the value of multi-parametric magnetic resonance imaging (MP-MRI) scans for men who have been recommended for a prostate biopsy. There are two possible improvements that we are looking at. Firstly, we want to know whether MP-MRI scans can be used to help advise men whether or not they might safely avoid having a biopsy at all. Secondly, we want to know whether MP-MRI scans can help us to do better biopsies for men who choose to have them.

Standard biopsies can miss prostate cancers completely, or they may underestimate how serious the cancer is. In this study, a more thorough biopsy called Template Prostate Mapping (TPM) will be used in addition to the standard biopsy to assess the prostate as accurately as is possible. We will also give each person an MP-MRI scan, so that we can compare the results of the scans with the more accurate biopsies.

2. What is the prostate?

The prostate is a male gland that sits just below the bladder (See Figure 1). The prostate produces fluid that forms part of the semen and may help nourish sperm. When you empty your bladder, urine flows through a tube (the urethra) that passes through the prostate before reaching the penis.

Figure 1: Location of the prostate



3. What is a biopsy and how does it diagnose prostate cancer?

We diagnose prostate cancer using a standard biopsy, which is also called a TRUS guided biopsy. This is a procedure in which a doctor uses needles to take samples from the prostate gland. The doctor places an ultrasound probe in your rectum (your “back passage”). This probe produces pictures to guide needles (usually 10 or 12) through the rectum and into the prostate. The doctor uses the ultrasound picture of the prostate to make sure the needles are spread equally around the prostate. We call this procedure a TRUS guided biopsy because TRUS stands for **T**rans **R**ectal **U**ltra **S**ound. We carry out standard TRUS biopsies using a local anaesthetic, and it takes around 10 to 15 minutes to complete. It can be uncomfortable and there is a small risk of side effects such as infection (see Table 1 page 9). The samples obtained from the prostate are looked at under a microscope to see whether or not cancer is present.

TRUS biopsies, which are currently used as standard care, can miss important cancers. TRUS biopsies are also believed to sometimes pick-up cancers that may not have affected the patient during their life-time, had they never been discovered in the first place. This is known as over-diagnosis. If these cancers are treated it is likely that little or no benefit will be had. When this happens we call it ‘over-treatment’.

TRUS biopsies can also give a false impression of how much cancer there is and how aggressive the cancer looks under a microscope. This is because the biopsies may not have sampled the main part of the cancer area. As a result, men can often undergo repeat biopsies every 1 or 2 years.

TRUS biopsies are the current standard biopsy for diagnosing prostate cancer. This study will be looking at this and other procedures for diagnosing prostate cancer, shown in section 7 below.

4. Why have we invited you to take part in this study?

We have invited you to take part because your doctor has recommended that you have a prostate biopsy. Approximately 720 men from the UK will take part in this study.

5. Do I have to take part?

No. It is up to you to decide whether or not to take part. If you decide to take part we will ask you to sign the consent form attached to this sheet, and we will give you a copy of the information to keep. You will have as much time as you need to decide. If you decide to take part, you are free to withdraw at any time without giving a reason and without affecting the care you receive in the future. If you choose not to take part then your doctor will explain the best standard care available.

Please note, if you have a pacemaker or have had any hip replacement surgery, you will not be able to have an MRI scan and so you cannot take part in the study.

6. What is the standard care?

The standard care at the moment is to have a TRUS biopsy, as detailed in section 3.

7. What are the other procedures for diagnosing prostate cancer that are being looked at in this study?

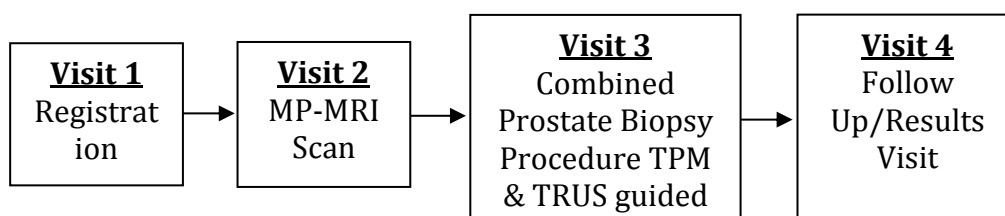
- **MP-MRI** stands for **M**ulti **P**arametric **M**agnetic **R**esonance **I**maging. This type of scan does not use radiation. As in standard MRI, MP-MRI uses magnetic signal to build up a picture of your prostate. However, in addition to this, MP-MRI uses additional types of magnetic signals to build up images of the prostate tissue such as how dense the cells are and how much blood flows through different parts of the prostate. This gives an overall assessment of your prostate. It is believed the MP-MRI approach increases the accuracy of the scan result but we cannot be sure of this without doing this study.
- **TPM** – Stands for **T**emplate **P**rostate **M**apping. This is a biopsy that involves taking samples of the prostate through the outer skin between the rectum and scrotum rather than through the inside of the rectum. The number of samples to be taken depends on the size of your prostate. Typically doctors take around 50-60 samples in order to thoroughly sample and map the entire prostate, but in some cases it can be more or less than this. We usually carry out TPM under a general or spinal anaesthetic.

The men in the study will have these extra procedures as well as the standard TRUS guided biopsy, so that we can compare all the results to see which are the most accurate for diagnosis and which are the most helpful for planning treatment.

8. What will happen to me if I take part in the study?

Once you have talked about the study with the research team and after you have signed the consent form, we would need to assess you in order to see whether you fit the entry criteria for the study. If it has not been done already, we will take blood and urine samples and perform a digital rectal examination (see section 11b for description) at your first visit to assess your baseline details such as PSA level, which will help with your diagnosis. If you have agreed on the consent form for additional blood and urine samples to be taken, these will be taken at this point. If you fit the entry criteria, we will register you to the study (Visit 1) and invite you to have an MP-MRI scan of your prostate (Visit 2) (See Figure 2). After your scan, we will carry out one combined biopsy procedure (TPM and TRUS guided biopsy) under the same anaesthetic (Visit 3). A follow-up visit will occur after the biopsies where your results of all procedures will be given to you (Visit 4). At this stage your participation in the study will be over.

Figure 2: Trial diagram



a) MP-MRI scan

We do MP-MRI scans with you lying flat on your back on a bed that moves through a scanner. A radiographer controls the scanner, and he or she can see, hear and talk to you at all times. In order to get the best pictures of the prostate we will inject you with a contrast agent (or “dye”). We inject this contrast agent into your arm, which can sometimes make your arm feel warm. A medication called Buscopan is injected into your vein to slow bowel movements. A moving bowel can reduce the quality of the images produced by the MRI. The whole scan should take about 30 to 40 minutes. During the scan we will ask you to lie as still as you can. We can offer you music to listen to using headphones, if you wish.

If you are anxious about the scan feel free to ask any questions. We can arrange for you to visit the scanner beforehand if you wish. You can also find information about MRI scans on the website www.macmillan.org.uk, or by ringing Macmillan Cancer Support on freephone 0808 808 0000.

b) Combined prostate biopsy procedure

The combined prostate biopsy procedure should take place within 3 months of the MP-MRI scan. To prepare you for the procedure, you will be prescribed a tablet called an alpha-blocker (such as tamsulosin or alfuzosin). This type of tablet relaxes the prostate and reduces the chance of problems passing urine after the procedure. You should continue taking these tablets for two weeks after the procedure.

We will also give you antibiotic tablets and antibiotic injections at the time of the anaesthetic (see appendix 1).

You will need to come into hospital a few hours before the biopsy procedure. You should not eat anything for 6 hours before the biopsy and you can drink only water up to 4 hours before the biopsy. The anaesthetist will see you before the procedure to discuss the anaesthetic with you.

The combined prostate biopsy procedure (TPM + TRUS) takes around 50 to 60 minutes. We do it under general or spinal anaesthetic. Once you are anaesthetised an ultrasound probe is gently inserted into your rectum. A soft flexible tube, called a catheter, is inserted through your penis into your bladder. Both the ultrasound probe and catheter are placed whilst you are under anaesthetic. After the procedure, it is likely that your doctor will keep the catheter in place for about 7 to 10 days. This is to make sure that in the period needed for your prostate to recover you are able to pass urine comfortably. The catheter does not need to be connected to a bag at all times and will not interfere with most of your daily activities. Your doctor will explain with further detail when you visit the trial team. We will arrange for you to come and have your catheter removed in hospital.

TPM involves a biopsy of the prostate done through a grid (template). The grid has holes every 5mm, which we place against the skin between the scrotum and rectum. This approach allows us to biopsy the whole of the prostate. At the beginning of the procedure we inject your skin with local anaesthetic. At the end of procedure, we place a dressing over the area. Immediately following this and whilst you are still anaesthetised we

clean the back passage with an anti-septic solution and then we will do a TRUS guided biopsy.

c) After the combined prostate biopsy procedure

It is normal to spend about 20 to 30 minutes in the recovery area after an anaesthetic. Once you have fully woken up we will transfer you to the ward. Once you feel steady on your feet we will allow you to go home. You will need to be accompanied on your journey home. Most men are ready to go home within 2 to 4 hours of the procedure. Before going home we will make sure you have enough antibiotics and alpha blockers. We will also prescribe pain killers in case you experience pain or discomfort after the procedure. However, pain is unusual and most patients are comfortable either with no pain killers or with something like paracetamol or an anti-inflammatory.

Any prostate biopsy can lead to infection; this is why it is very important that you take the antibiotics that you are given. Infection that is left untreated can be a very serious complication.

If, after the biopsy, you experience a fever, or any other symptoms of concern, it is extremely important to head directly to the closest accident and emergency department. Inform them that you had prostate biopsies and show them your patient card. Then contact your study hospital (using the details at the end of this information sheet or on your patient card). You must make contact so that any complications may be treated promptly before they become serious.

You can usually return to work the day after the procedure. It may be difficult sitting down for prolonged periods for the first 2 to 3 days. Before driving, you need to check with your insurance company about your cover following a general or spinal anaesthetic. You also need to feel comfortable doing an emergency stop. If you are taking any medication, check with your pharmacist whether it is safe to drive while taking them.

Neither you, nor your study doctor, will be given the results of the MP-MRI scan until approximately 4 weeks after the biopsies, when you will get all your results at a follow-up clinic visit. At this stage your participation in the study will be over

and depending on your results, you will discuss future treatment options with your clinician.

9. What are the alternatives?

If you choose not to take part in the study then your doctor will recommend that you have a TRUS guided biopsy, without the study procedures i.e. without the MP-MRI or the additional TPM.

10. Can I change my mind?

Yes, you can change your mind at any time after you consent. Depending on when you change your mind, your doctor will recommend that you continue with standard care which could be a TRUS guided biopsy, without the MP-MRI or the additional TPM. Your doctors could also recommend that you undergo the TPM biopsy.

If you choose not to enter this study and you have a prostate biopsy as your standard care, you cannot then change your mind and enter the study.

11. What else will I have to do?

a) As part of the PROMIS trial

If you choose to participate and enter the study, you will make some extra visits to hospital:

- To assess your suitability for the study, and that you wish to take part. You will be asked to sign a consent form
- For the MP-MRI scan
- For a combined TRUS guided biopsy and TPM procedure under general or spinal anaesthetic. You will also be required to attend either another visit or a telephone call with a nurse at the hospital to assess your fitness for a general or spinal anaesthetic.

b) Additional optional research requests

In addition to the initial blood and urine tests, we will ask you to provide extra samples to be collected and stored for research (100 ml of blood (just under half a cup) and up to 250 ml of urine (one cup)). We will ask for urine samples before and after a back passage examination (also known as a digital rectal examination). The first sample before this examination can be given at any time. You will then be asked to drink more water. Once your bladder feels full, the researcher will carry out the digital rectal examination. During this, the researcher will put a gloved

finger into your back passage (rectum) and gently stroke the prostate to feel your prostate gland. You will then be asked to provide a urine sample. If you take part in PROMIS, we would like your permission to use these stored blood and urine samples for prostate cancer research. These research studies are not expected to benefit you, but may help to improve the diagnosis and/or the treatment of prostate cancer for future patients.

Any extra blood and urine samples that you give us for these research studies will be stored securely for several years, so that we can repeat any tests on them if necessary, and evaluate new tests for prostate cancer. These samples will be identified using a special study number assigned to you, in such a way that the scientists analysing them will not be able to find out your identity.

This research would be carried out only after approval from an independent research ethics committee and would involve extracting DNA or other chemicals from the samples to see whether the tests make it is easier to detect prostate cancer. These samples would be considered a gift from you and no personal results from these tests or studies could be provided to you.

A MP-MRI scan is performed as part of this study. A 3-dimensional Ultrasound is performed as part of the biopsy procedure. We would also like to know if you are willing for us to store and use your MP-MRI and Ultrasound imaging data to see if new ways of looking at these scans can detect cancer better in the future.

We would also like to know if you are willing for us to record and store your full postcode. This part of the study is optional. The postcode will be used to study socioeconomic status of PROMIS participants. Your postcode will be collected at study registration and kept confidential in a secure password protected database.

We will also ask if you are happy to be contacted within 5 years to see if you would be willing to fill in a questionnaire about your health status (including details of any other biopsies you have had since the study) and your quality of life. If you do decide to take part a member of the PROMIS research team may send this request to your home address.

12. What are the possible disadvantages and unwanted side effects of the study?

If you do take part in the PROMIS study, you will need to attend some extra hospital visits. There are possible side effects associated with the study procedures, which are detailed below. We will monitor you for these side effects and you may need to take additional treatment to control any that develop. For more information see Table 1 on page 9.

Possible side effects

a) MP-MRI

MRI rarely has any side effects. Some men find the scanner claustrophobic. Putting a cannula (plastic needle) in the arm (to inject the contrast agent – see Part 1 section 8a above) 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. Staff are trained and will be on hand to deal with this if it does occur.

b) Anaesthetic

Bruising of the skin from intravenous catheters is common. Less common side effects include skin infections from intravenous catheters affects, nausea or vomiting, a dry cough and a sore throat. These side effects are temporary.

The risk of death under anaesthesia in the UK is very low (1 in 150,000 anaesthetics).

c) Combined prostate biopsy procedure

Both biopsy procedures carry risks and complications (See Table 1 on page 9).

These are similar but there are two important differences:

- TPM is cleaner than TRUS guided biopsy and has a lower infection rate because the needles are going through skin rather than rectum.
- TPM takes more samples than TRUS guided biopsy, so there is more bruising and the prostate can swell resulting in difficulty passing urine because the water passage can become blocked.
- In standard care, TRUS guided biopsies are done without men being asked to empty their back passage or without any cleansing of the back passage. In the PROMIS study we ask you to empty the back passage with enemas or suppositories. In addition, we cleanse the back passage with anti-septic solution during the procedure in order to reduce the risk of infection.

If you are concerned about possible side effects you can find the 24 hour emergency contact details for your study hospital at the end of this information sheet (Part 2 section 9).

There is no evidence that having multiple biopsies raises your chances of prostate cancer spreading.

Table 1: Possible side effects of the combined biopsy procedures compared to standard TRUS guided biopsy

Procedure Side effect	TRUS alone (standard care)	Combined biopsy: TPM +TRUS (in the PROMIS study)
Pain/Discomfort	Almost all men experience temporary discomfort in the rectum	Almost all men experience temporary discomfort in the rectum
Burning when passing urine	Almost all men	Almost all men
Bloody Urine	1 in 2 men (self-resolving, 2-3 days)	Almost all men (self-resolving, 2-3 days)
Bloody Sperm	3 in 10 men (2-3 months to resolve)	Almost all men (lasting up to 3 months)
Poor erections	3 in 10 men (self-resolving after 6-8 weeks). Rarely, tablets may be needed to help the erections improve.	Almost all men (self-resolving after 6-8 weeks). Rarely, tablets may be needed to help the erections improve.
Infection of skin or urine	1-8 in 100 men	1-8 in 100 men
Infection of skin or urine requiring admission and intravenous antibiotics	Between 1-4 in 100 men	Between 1-4 in 100 men
Difficulty passing urine*	1 in 100 men	1-3 in 20 men.
Bruising of skin	None	Almost all men
Bruising spread to scrotum	None	Between 1 in 20 to 1 in 10 men

A catheter is usually placed temporarily as otherwise the urine flow may stop suddenly, requiring a visit to the A&E department. To avoid this, your doctor is likely to keep your urinary catheter in place for about seven to ten days after the procedure as explained above (Section 8.C). Most find the catheter tolerable although some discomfort can be felt. Rarely, there may be on going discomfort which is controlled by medications.

13. What are the possible benefits to me and for others of me taking part?

Because the TPM biopsy is more thorough than TRUS guided biopsy, if you do have prostate cancer, it is more likely that it will be diagnosed. The size and features of any prostate cancer can also be assessed in more detail. This makes it easier to choose the most appropriate treatment because the TPM gives more information about the risk that a particular cancer poses to an individual man.

Alternatively, if all the tests in this study come back normal, you can be reassured you do not have prostate cancer (unlike after a normal TRUS guided biopsy only). It is therefore less likely that you will need to have another prostate biopsy in the future.

If you decide not to take part in the study, and prostate cancer was found during the TRUS guided biopsy, you will receive the standard care available at your hospital. Some hospitals offer an MRI scan as standard care to those men diagnosed with prostate cancer on biopsy in order to provide a more detailed picture of how advanced a cancer is. If you do take part in the study you will undergo an MP-MRI scan before the biopsies. There are two main benefits of this. Firstly, MP-MRI scans are clearer to read before, rather than after, biopsy procedures and secondly, if you do need treatment, it may be possible to start treatment sooner.

In addition, the PROMIS trial could mean that, in the future fewer men will need to be biopsied, and that biopsies will be more accurate.

14. What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed individually. You can find more detailed information on this in Part 2 section 2 of this information sheet.

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

Yes, all the information about your participation in this study will be confidential. The details are included in Part 2 section 3.

16. What happens when the study stops?

It is also important for us to know how you are doing even after your participation in the study has stopped so we can follow up on your health status to help future related research. For this reason, we will ask for your consent for your name to be used to gather information from records held by the NHS and maintained by the NHS Information Centre and the NHS Central Register or any applicable NHS information system (including linkage to routine hospital admission data). In order for us to do this we provide identifiable information for us to trace you on the National Health Service Care Register (NHSCR) (this is an optional part of the study).

This completes Part 1 of the information sheet. If you are considering participating in the study, please continue to read the additional information in Part 2 before making your decision.

PART 2

1. What happens if relevant new information becomes available?

Data from this study will be monitored regularly by scientists who are independent of the study. Sometimes, during the course of a research project, new information becomes available about the procedures that are being studied. If you are in the study and this happens, your study doctor will tell you about it and discuss with you whether you want to, or should, continue in the study. If you decide not to carry on, your study doctor will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign a consent form that includes new information. Also, on receiving new information your study doctor might consider it to be in your best interests to stop the medical procedures in the study. If so they will explain the reasons and arrange for your care to continue another way. If the study is stopped for any other reason, you will be told why and your doctor will arrange for your continuing care. If any relevant new information becomes available after you have had all of your procedures and you have received your results, it will not affect you as you will no longer be in the study. The maximum amount of time we expect participants to spend in this study is 3 to 4 months. For most it will be significantly less.

As described earlier, you can stop taking part in the study at any time without giving a reason and without your rights or care being affected in any way. If you do decide to withdraw then you should inform your doctor of your decision so that appropriate follow up can be arranged. If you do withdraw, your doctor may still recommend that you undergo biopsies of the prostate including TPM biopsies as standard care.

We expect this study to run for two or three years, whilst we recruit the 720 volunteers, carry out all the procedures and assess all the results. We are not aware of any similar studies being carried out anywhere else in the world, and so it is unlikely that new information will come available that will affect this study. The aim of this study is to provide new information about the procedures involved to find the most accurate way of diagnosing prostate cancer in future, across the world.

2. What if there is a problem?

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

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

Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated by members of staff or about any side effects (adverse events) you may have experienced due to your participation in the clinical trial, the normal National Health Service complaints mechanisms are available to you. Please ask your study doctor if you would like more information on this. Details can also be obtained from the Department of Health website (<http://www.dh.gov.uk>).

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

All data will be identified by a number only which can link to your other details. This link will be held separately from all other data collected on you. If you consent to take part in this study, we will collect information on you, your disease and your results, and we will enter it onto a study database. This is for the purposes of analysing the results. Scientific and medical employees of the Medical Research Council Clinical Trials Unit (MRC CTU) and people from University College London (UCL/UCLH) Joint Biomedical Research and Development Unit may need to examine your medical records to ensure the study is being run properly, but your confidentiality will be protected at all times, and your name will not be disclosed outside the study. Your information may also be looked at by an independent quality control agency to check that the study is being carried out correctly.

You will be asked to give consent to allow potential future contact so that you may be sent questionnaires on health status and quality of life. If you consent to this, a letter may be sent to your home addresses. Your name and address would be kept separately from the study database to keep the study data collected anonymous. This consent is optional and does

not affect your right to take part in the rest of the study. Ethical approval would be sought for future research involving the use of questionnaires.

The MRC CTU and UCL are registered under the [UK] Data Protection Act to hold such information on a confidential basis. An independent expert committee will confidentially review the study at regular intervals. This is so that if new evidence comes to light or that evidence from within the study clearly shows that one of the procedures gives substantially better or worse diagnoses than the other, then the study could be stopped early, though your care will continue. This expert committee will also monitor the safety of the procedures within the study. No individual patients will be identified when the study results are published.

4. Involvement of your General Practitioner (GP)/family doctor

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

- 1.
- 2.

5. Additional Research: Health Economics

A further part of this study is to find out the cost effectiveness of having the MP-MRI scan instead of, or as well as, the other two biopsies. To help with this we will ask you to fill in a questionnaire about your health.

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

When the study is completed the results will be analysed and presented at international meetings before being published in a medical journal. Large studies such as this take many years to complete and for the final results to appear, although we expect to have the results from this study available in summer 2014 or possibly sooner. If you wish to receive information on these results when they are presented please ask your study doctor. We will also publish a summary of the results on the MRC CTU web site (<http://www.ctu.mrc.ac.uk/>).

7. Who is organising and funding the research?

The study is funded by the National Institute for Health Research, Health Technology Assessment (NIHR HTA) programme and is supported by the National Cancer Research Network (NCRN). NIHR HTA and the NCRN receive money from the government, charities and industry. The sponsor of the trial is UCL and they have delegated the study to be managed and run by the MRC.

None of the doctors or other staff conducting the research are being paid for recruiting patients to the study or for looking after patients in the study.

8. Who has reviewed the study?

The study has been reviewed by independent international experts, the National Institute for Health Research, Health Technology Assessment (NIHR HTA) and the National Cancer Research Network (NCRN). The study has been approved by the NRES Committee London – Hampstead.

Three cancer patient representatives have been involved in reviewing the study within the NCRN, two cancer patients have helped work on the design on this study, and all three cancer patient have helped write this information sheet.

9. Contacts for further information

If you would like further information or have any questions about this study please discuss them with the research staff or your study doctor.

PROMIS research staff contact details:

<please insert contact details>

PROMIS study doctor contact details:

<please insert contact details if different from above, otherwise please delete>

You may also find it useful to contact Macmillan Cancer Support, an independent patient advisory group (www.macmillan.org.uk, freephone 0808 808 0000; address: 3 Bath Place, Rivington Street, London, EC2A 3JR) or the Cancer Research UK website (www.cancerresearchuk.org). Macmillan Cancer

Support includes the information and helpline formerly provided by CancerBACKUP.

If you would like to know more about how patients help initiate, design, support and monitor research, you will find information on the websites for the NIHR (www.crncc.nihr.ac.uk), the NCRN (www.ncrndev.org.uk) or the NHS (www.invo.org.uk)

Any prostate biopsy can lead to infection; this is why it is very important that you take the antibiotics that you are given. If infection is untreated this can be a very serious complication. **If, after the biopsy, you experience a fever, or any other symptoms of concern, it is extremely important to contact your study hospital immediately (using the emergency details below).** You must make contact so that any complications may be treated promptly before they become serious.

Your emergency 24 hour contact numbers are:

<please insert emergency contact details>

We will give you a copy of this information and a copy of the signed consent form to keep.

Thank you for taking the time to read this information about the study.

Appendix 1

Your doctor will be giving you a prescription containing these medications after reviewing your medical history. **Unless told otherwise** by your trial doctor you should use the medications prescribed as follows:

- **Tamsulosin or alfuzosin:** (prostate relaxer) – start taking this medication one week before your biopsy and continue taking it for two weeks after your biopsy. Tamsulosin and alfuzosin can make you feel light-headed upon standing so we ask you to take it at night before you go to bed. If the feeling of light-headedness on standing up continues during the day then please stop taking the tablets and contact one of the trial team.
- **Ciprofloxacin:** (antibiotic) – start taking the night before your biopsy and also on the morning of the biopsy. Continue taking twice a day until you finish the course that has been given to you.
- **Phosphate enema:** please use this the evening before your biopsy. If you find that the enema does not help with opening your bowels or you are unable to use the enema for any reason then take one of the glycerine suppositories we have given you the night before the procedure.
- **Glycerine Suppository:** We will give you two of these suppositories. Use one if the enema has not worked the night before (see above). Please bring the second glycerine suppository to the hospital with you on the morning of the procedure and use it immediately when you arrive. The reason you should do this in the hospital is to avoid loose motions on your way in.

14.2. Appendix II

14.3. Standard operation procedures

14.3.1. Combined prostate biopsy

14.3.1.1. Main phase



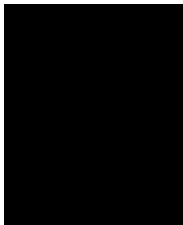
Developed with the NCRI Prostate Clinical Studies Group
Part of the NIHR National Cancer Research Network Portfolio
ISRCTN Number - 16082556
UCL reference – 11/0009
REC reference – 11/LO/0185

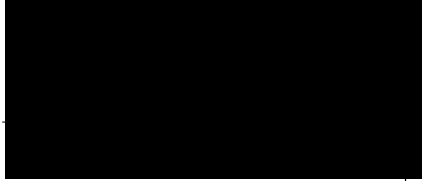



Evaluation of multi-parametric magnetic
resonance imaging in the diagnosis and
characterisation of Prostate Cancer

Combined Prostate Biopsy Standard Operating Procedures

v03.00 16SEPT2013

Authors		
Hashim Ahmed Co-Chief Investigator	Signature: 	Date: 16 th September 2013

Ahmed Shater Bosaily Research Fellow	 Signature:	Date: 16 th October 2013
Reviewed and Authorised by		
Mark Emberton Chief Investigator		Date: 17 th September 2013

Revision History

Version	Author	Date	Reason for Revision
01.00 – 01.01	Hashim Ahmed & Mark Emberton	5 th March 2012	<ul style="list-style-type: none"> - Version number and date - Included PROMIS logo - Use of Haematoxylin to stain the cores before they are put into the cassettes. - Clarified when the MP-MRI can be un-blinded. - Inserted new TPM and TRUS proforma into appendix 1 & 2.
01.01 – 02.00	Hashim Ahmed	1 st August 2012 – 6 th September 2012	<ul style="list-style-type: none"> - Version number and date - Prescription at time of consent for phosphate enema, two glycerine suppositories, alpha blocker and ciprofloxacin. - Time two glycerine suppositories should be taken the evening before and on the morning on the day of the procedure. - Dose of Amikacin 7mg/kg - Additional medications: Dexamethasone 0.15mg/kg and Lactulose 10ml tds/prn. - Changes to description for preparing materials. - Filter paper replaces blue/green sterile theatre

			<ul style="list-style-type: none"> drapes. - Figure 5 changed to show filter paper. - Clarifications to Barzell zone system sampling description. - Reminders on biopsy gun needle cleaning. - TRUS biopsy placement of cores in cassettes. - Stain TRUS biopsies with 20% Haematoxylin. - Advice for large glands and placement of catheter. - Copy of patient consent form to be placed in histology bags.
02.00 – 03.00	Hashim Ahmed & Shater Bosaily	<i>25th June 2013 – 16th September 2013</i>	<ul style="list-style-type: none"> - Version number and date - TPM part of SOP changed from 20 zone sampling, every 5mm with identification and orientation for every sample to, 20 zone sampling every 5mm, but no identification or orientation. - Bowel preparation instructions clarified. - 3D ultrasound no longer required. - Formalin pots to be used to prepare samples. - Removed pictures relating to multiwell cassettes, as well as those relating to inking and orientating cores. - Filter paper no longer required. - 20 zones modified Barzell zone diagram inserted. - New TPM proforma for 20 zones inserted, previous TPM proforma deleted. - Clarification that all UCLH

			<p>samples should stay at UCL and other centres should send TPM to UCLH, TRUS to be processed locally.</p> <ul style="list-style-type: none"> - Guidance on limited TPM added.
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1. Combined Biopsy: Conduct and items required

This procedure should be performed by a competent physician trained and certified according to the PROMIS protocol. The physician should be blinded to the MR imaging and other imaging as well as any reports. Any radiologists reporting or who have seen the MRI report should not be present at the time of the procedure.

The following documentation should be completed for every PROMIS patient entering theatre

- A PROMIS combined prostate biopsy checklist, case report form 3a (in your PROMIS patient file)
- TPM proforma (in your site file)
- TRUS proforma (in your site file)
- Histology request form (Use local request form)

The procedure will be carried out under general or spinal anaesthesia.

- At the time of consent
 - A prescription for a phosphate enema, 2 glycerine suppositories, an alpha-blocker and ciprofloxacin should be given to the patient.
- 7 days prior to the procedure
 - Anti-platelet agents (e.g. aspirin or clopidogrel) should be stopped. Anticoagulants (e.g. warfarin or heparin) should be stopped after consultation with local guidelines/haematologists.
 - An alpha-blocker (e.g. tamsulosin or alfuzosin) should be started, unless patient is on an alpha-blocker already. This should be continued for at least 2 weeks post-biopsy.
- Bowel preparation
 - A phosphate enema should be administered prior to procedure. This should ideally be administered at home, the evening prior to the procedure. If this cannot be done at home, then a phosphate enema or glycerine suppository can be given on the morning of the procedure by nursing staff on admission at least 30-60 minutes prior to procedure.
 - If the phosphate enema cannot be taken by the patient the night before, he should use one glycerine suppository the evening prior to the procedure. This will help with emptying of bowels, to reduce faeces.

- One glycerine suppository should be taken by the patient early in the morning on the day of procedure when they arrive in hospital, unless they have been given a phosphate enema on the morning.

Venous Thromboembolism Prophylaxis

This should be performed as per local guidelines. Compression stockings as a minimum.

Antibiotic regimen

- a) CIPROFLOXACIN 500MG twice daily with the first dose given the evening prior to the combined biopsy and then to be continued for 5 days.
- b) AMIKACIN 7mg/kg or GENTAMICIN 160mg (if local microbiology guidelines prevent use of amikacin) on induction.
- c) METRONIDAZOLE 1g suppository to be given immediately after TRUS guided biopsies.

Additional Medications

- a) Dexamethasone 0.15mg/kg to be given at induction by the anaesthetist.
- b) Lactulose 10ml tds/prn to be given after the biopsy.

Catheterise the patient with a 16Ch or 14Ch catheter under sterile conditions



(figure 1)

Figure 1. Equipment for catheterising

Items required:

Chlorhexidine for cleaning perineum
Leg and lithotomy drapes
Disposable 17G Template grid
2 x 17G biopsy guns
20ml syringe with 20ml Bupivacaine + Adrenaline injection BP 0.5% w/v, 1 in 200,000
Sterile gauze (blue and white)
Large Gallipot with sterile water
Large Gallipot with normal saline
Large Gallipot with Chlorhexidine solution
24 formalin pots
4 multiwell cassettes

2. Template Mapping Biopsies

Preparation of the template grid:

- i. Prepare the ultrasound probe. Place a small amount of ultrasonic gel into Endocavity balloon
- ii. Slide **Endocavity balloon** over probe and inflate balloon with water from a 50ml luer-lock syringe. Remove all air bubbles. Ensure the images are clear and without artefacts on both axial and sagittal views.
- iii. Mount ultrasound probe onto stepper platform.
- iv. Patient in lithotomy position.
- v. Place urethral catheter 14Ch or 16Ch and spigot outflow.
- vi. Lift scrotum and fix with adhesive dressing.
- vii. Clean perineum with chlorhexidine 2%.
- viii. Inject 20ml Bupivacaine + Adrenaline injection BP 0.5% w/v, 1 in 200,000 to perineal skin.
- ix. Place **stepper** mounted ultrasound probe into rectum.
- x. Use **DISPOSABLE Template Grid** (See figure 2 below) (Accucare or suitable alternative) (5mm spaced, 17G holes) with upper case letters facing the operator.



Figure 2 – Disposable Template Grid

- xi. Align prostate so that urethra is on 'D' and ensure that the whole prostate is covered with the sampling grid-holes. Ensure that the full length of the prostate fits into the sagittal view with ultrasound probe fully inserted. 'Run-through' prostate with axial views to ensure prostate is positioned with midline on urethra and whole prostate covered by grid. If pubic arch prevents biopsy of lateral and anterior areas, the legs can be raised and the ultrasound probe repositioned.

- xii. Biopsy protocol (please see pages 9 - 10).

NB: at this point make a judgement as to whether the prostate can be fully biopsied using the Template Mapping Biopsy procedure. The main reason why Template Mapping Biopsies may not be of sufficient quality is due to prostate size and/or dimensions:

- i. if the anterior and lateral parts of the gland lie behind the pubic arch and raising and hyper-extending the legs still does not allow full gland sampling.
- ii. if median lobe is large, preventing adequate sampling.
- iii. if sagittal length of prostate is too long to allow adequate sampling with two throws of the needle (apical and basal).

If a judgement is made that template biopsies will be inadequate then a limited TPM can be conducted (**for information regarding limited TPM please see page 10**). If a limited TPM will not be possible then only a standard set of TRUS biopsies should be taken.

After the procedure, the patient should be informed that a limited TPM was conducted or only a standard set of TRUS biopsies could be performed.

If only a standard set of TRUS biopsies could be conducted the patient must also be informed that they have been partially withdrawn from the study. A withdrawal form must be completed and returned to the MRC CTU immediately. The time point at which the patient withdrew from the study should be marked as after MP-MRI and before combined prostate biopsy procedure.

Please note:

Under no circumstances can the MR-imaging be un-blinded. Results of the MR-imaging can only be un-blinded after the TRUS (and limited TPM) results are available, regardless of whether or not the patient has been withdrawn from the study.

Preparation of material:



Figure 3:
preparation of
equipment prior to

Have 20 formalin

biopsy
pots

ready for biopsy collection. Using a surgipath pen label the formalin pots with the respective number for the Barzell zones, 1 to 20.

TPM Biopsy Protocol:

The Modified Barzell Zone system should be used (please see figure 4 below) and a PROMIS TPM proforma should be completed (see appendix 1).

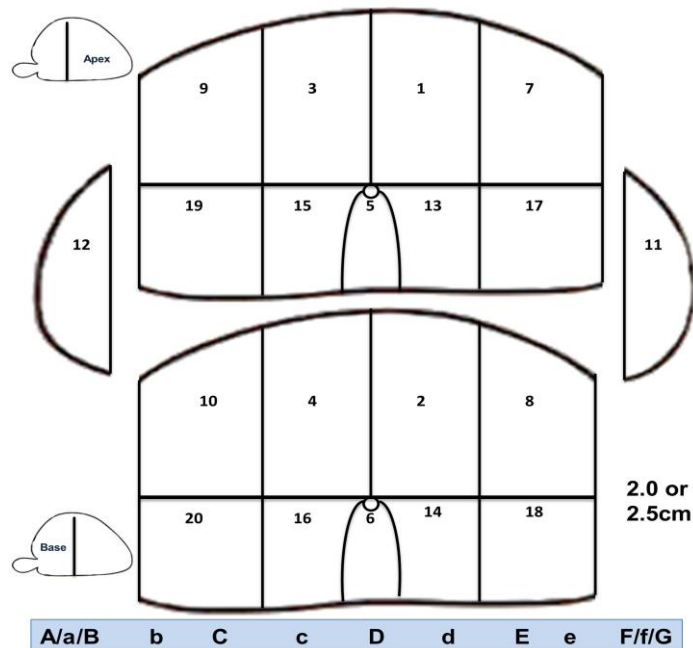


Figure 4:
Modified
Zone System

Barzell

Biopsies are to
taken in a zonal
There is no need
orientate or

individually identify each template biopsy core. Simply insert the biopsy from the biopsy

be
fashion.
to ink,

gun into the formalin pot.

If the z axis is short then the operator still needs to make an attempt to take an apical and basal core by dividing the prostate into two in the sagittal plane. Continue in this fashion for all zones except zones 11 and 12 which should be sampled one at a time.

- Ensure that the biopsy gun needle is cleaned with Chlorhexidine 2% solution then rinsed with normal saline in between every core sample
- Fill out the Pathology TPM proforma (appendix 1) so that an accurate record can be kept of the biopsies.

Using a rolled up swab soaked in chlorhexidine 2% insert into rectum to clean. Repeat 2 or 3 times.

After Template Mapping biopsies are complete, apply blue gauze pressure dressing with appropriate adhesive tape. This can be removed after a day or until it starts to fall off.

Limited TPM

Biopsies are to be taken in a zonal fashion. There is no need to ink, orientate or individually identify each template biopsy core. Simply insert the biopsy from the biopsy gun into the formalin pot.

Only between two – three samples should be taken from each zone in a well-spaced manner.

If the z axis is short then the operator still needs to make an attempt to take an apical and basal core by dividing the prostate into two in the sagittal plane. Continue in this fashion for all zones except zones 11 and 12 which should be sampled one at a time.

- Ensure that the biopsy gun needle is cleaned with Chlorhexidine 2% solution then rinsed with normal saline in between every core sample
- Fill out the Pathology TPM proforma (appendix 1) so that an accurate record can be kept of the biopsies.
-

After Limited Template Mapping biopsies are complete, apply blue gauze pressure dressing with appropriate adhesive tape. This can be removed after a day or until it starts to fall off. DO NOT proceed to clearing the rectum with Chlorhexidine swabs or performing a TRUS.

3. Transrectal Ultrasound Guided Biopsies

- a) Leave patient in lithotomy position.
- b) Using a needle mount on the trans rectal probe, standard 12 core trans rectal biopsies are taken using the following protocol. A TRUS proforma should be used (see appendix 2).
 - A: Right lateral base
 - B: Right lateral mid
 - C: Right lateral apex
 - D: Right parasagittal base
 - E: Right parasagittal mid
 - F: Right parasagittal apex
 - G: Left lateral base
 - H: Left lateral mid
 - I: Left lateral apex
 - J: Left parasagittal base
 - K: left parasagittal mid
 - L: Left parasagittal apex
- c) Each core should be identified individually
- d) Place cores into multi-well cassettes with right and left identified separately. Ensure the multiwell cassettes are appropriately labelled with the biopsy location letter. Place cores ABC and cores DEF into two separate cassettes but in the same formalin pot (Right). Place cores GHI and cores JKL into two separate cassettes but in the same formalin pot (Left).

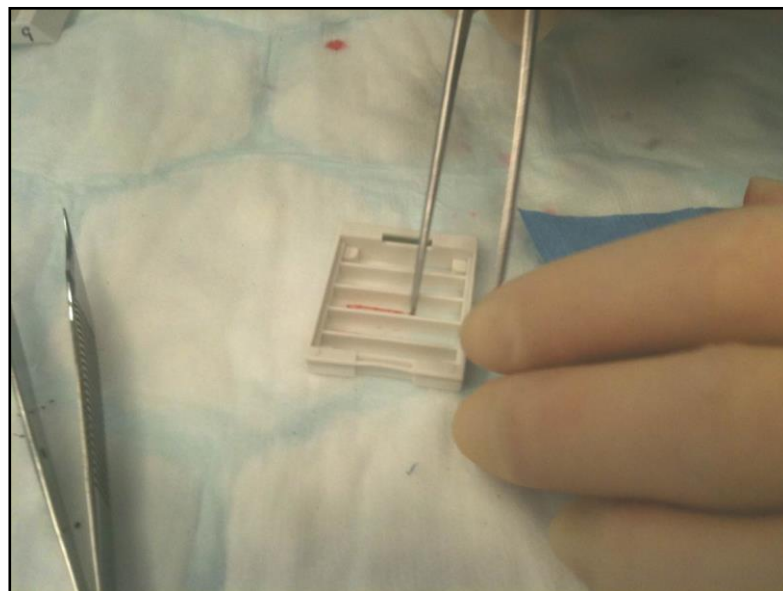


Figure 5: Placing cores into the cassette

- e) Inking the core is not necessary.
- f) Ensure that the biopsy gun needle is cleaned with chlorhexidine and then normal saline in between every core sample
- g) If 10 cores are taken then only two multiwell cassettes are needed.

- h) If 12 cores are taken then 4 multiwell cassettes are needed.
- i) Ensure urine is clear by opening catheter. If not, bladder washouts should be carried out until clear and/or a 20Ch-22Ch 3-way irrigating catheter left in with irrigation for 1-2 hours in recovery. Catheter can be removed prior to returning to ward but a catheter is usually required. This is at the operator's discretion. If the gland was large or if there are any concerns that there is likely to be urinary retention post-operatively, a catheter should be placed for the patient to go home with. This should be removed after a minimum of 3 days at the earliest trial-without a catheter (TWOC) clinic.

4. Labelling and sending biopsy samples from Template Mapping and TRUS biopsies to Histopathology

- a) **Template mapping:** Histopathology request forms should identify patient as a member of PROMIS, the PROMIS patient ID should be written in the section 'what information are you looking for from this biopsy?' or equivalent section on your local pathology request form. All formalin pots from a patient, PROMIS TPM proforma, a copy of the patient trial consent form and histology request form should be packaged together and clearly labelled using your standard patient sample labels.

These samples need to be transported by medical courier to University College Hospital, London.

University College London Hospitals NHS Trust Histopathology Department.

Addressed to: **Dr Alex Freeman, Consultant Histopathologist. Department of Histopathology, 4th floor, Rockefeller Building, 21 University Street, WC1E 6BT**

- b) **TRUS:** Histopathology request forms should identify patient as a member of PROMIS, the PROMIS patient ID should be written in the section 'what information are you looking for from this biopsy?' or equivalent section on your local pathology request form. All formalin pots, PROMIS TRUS biopsy proforma, a copy of the patient trial consent form and histology request forms should be packaged together and clearly labelled using your standard patient sample labels.

These samples can be transported to the local pathologist according to local standard operating procedures.

5. Processing of Biopsy samples at the Central UCLH laboratory

Please note, for non-UCLH centres, the TRUS biopsy should stay with the local pathologist for reporting. The template biopsies must be sent to UCLH.

- a) On arrival, the UCLH pathology laboratory must process the Template Mapping Biopsies and TRUS guided biopsies separately.
- b) Template Mapping Biopsies should be assigned to one of the two trial pathologists (Dr Charles Jameson or Dr Alex Freeman) for reporting. TRUS biopsies should be assigned to the other.
- c) There should be no communication with respect to a patient between the two reporting pathologists. In the case of uncertainty over an area on histology the third named pathologist should be consulted.
- d) The reporting proforma for the pathology of each zone will identify:
 - Location
 - Length of core (mm) or total length of all cores in the zone
 - Presence of cancer (Yes/No)
 - Primary Gleason grade (if cancer present)
 - Secondary Gleason grade (if cancer present)
 - Tertiary Gleason grade (if cancer present)
 - Amount of cancer (UK and ISUP) (mm) (maximum and total cancer core lengths)
 - Presence of severe inflammation (if no cancer) (Yes/No)
 - Presence of HGPIN (if no cancer) (Yes/No)
 - Presence of ASAP (if no cancer) (Yes/No)
- e) Information on zones will be recorded electronically in the MRC CTU electronic Macro database system.
- f) See the PROMIS reporting results to patients SOP for information on retrieving results.

Appendix 1 – TPM Proforma

Master TPM Proforma v02.00 30th July 2013

<<Insert local hospital logo here>>



Patient Initials:

PROMIS Trial Number:

Date of Birth:

Hospital Number:

Pathology ID Number:

1. Date of TPM Biopsy:

2. Was a limited TPM performed? ☐ 0 = No
☐ 1 = Yes

3. Insert number of cores taken per zone on the diagram below.

A/a/B	b	C	c	D	d	E	e	F/f/G
9	3	1	7					
19	15	5	13	17				
10	4	2	8					
20	16	6	14	18				

- 1 Left Parasagittal Anterior Apex
- 2 Left Parasagittal Anterior Base
- 3 Right Parasagittal Anterior Apex
- 4 Right Parasagittal Anterior Base
- 5 Midline Apex
- 6 Midline Base
- 7 Left Medial Anterior Apex
- 8 Left Medial Anterior Base
- 9 Right Medial Anterior Apex
- 10 Right Medial Anterior Base

- 11 Left Lateral
- 12 Right Lateral
- 13 Left Parasagittal Posterior Apex
- 14 Left Parasagittal Posterior Base
- 15 Right Parasagittal Posterior Apex
- 16 Right Parasagittal Posterior Base
- 17 Left Medial Posterior Apex
- 18 Left Medial Posterior Base
- 19 Right Medial Posterior Apex
- 20 Right Medial Posterior Base

Please do not send a copy of this form to the MRC CTU.

Appendix 2 TRUS Proforma

Master TRUS Proforma v02.00 30th July 2013



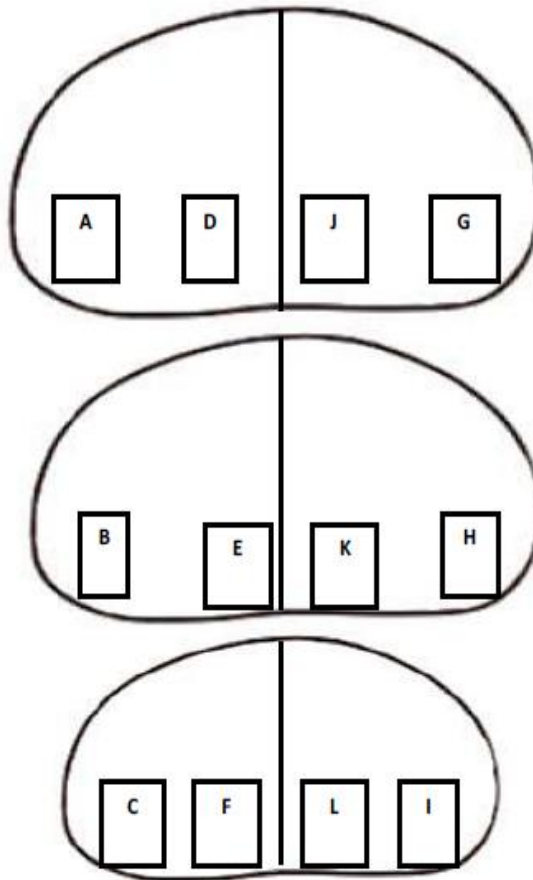
<<Insert local hospital logo here>>

[illegible]

Pathology ID Number:								
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1. Date of TRUS Biopsy:

d	d	m	m	y	y	y	y
---	---	---	---	---	---	---	---



A = Right lateral base	<input type="checkbox"/>	G = Left lateral base	<input type="checkbox"/>
B = Right lateral mid	<input type="checkbox"/>	H = Left lateral mid	<input type="checkbox"/>
C = Right lateral apex	<input type="checkbox"/>	I = Left lateral apex	<input type="checkbox"/>
D = Right para base	<input type="checkbox"/>	J = Left para base	<input type="checkbox"/>
E = Right para mid	<input type="checkbox"/>	K = Left para mid	<input type="checkbox"/>
F = Right para apex	<input type="checkbox"/>	L = Left para apex	<input type="checkbox"/>

Please do not send a copy of this form to the MRC CTU.

14.3.1.2. Pilot phase



Developed with the NCRI Prostate Clinical Studies Group
Part of the NIHR National Cancer Research Network Portfolio
ISRCTN Number - 16082556
UCL reference - 11/0009
REC reference - 11/LO/0185

PROMIS – Prostate MRI Imaging Study

Evaluation of multi-parametric magnetic
resonance imaging in the diagnosis and
characterisation of Prostate Cancer

Combined Prostate Biopsy Standard Operating Procedures

DV00.10 20FEB2012

Combined Biopsy: Conduct and Reporting

This procedure should be performed by a competent physician trained and certified according to the PROMIS protocol. The physician should be blinded to the MR imaging and other imaging as well as any reports. Any radiologists reporting or who have seen the MRI report should not be present at the time of the procedure.

The following documentation should be completed for every PROMIS patient entering theatre

- A PROMIS combined prostate biopsy checklist, case report form 3a (in your PROMIS patient file)
- TPM proforma (in your site file)
- TRUS proforma (in your site file)
- Histology request form (Use local request form)

The procedure will be carried out under general or spinal anaesthesia.

- 7 days prior to the procedure - Anti-platelet agents (e.g. aspirin or clopidogrel) should be stopped. Anticoagulants (e.g. warfarin or heparin) should be stopped after consultation with local guidelines/haematologists.
- At least 2 days prior to procedure - An alpha-blocker (e.g. tamsulosin or alfuzosin) should be started, unless patient is on an alpha-blocker already. This should be continued for at least 2 weeks post-biopsy.
- Bowel preparation - A phosphate enema should be administered prior to procedure. This should ideally be administered at home, the evening prior to the procedure. If this cannot be done at home, then it should be given on the morning of the procedure by nursing staff on admission at least 30-60 minutes prior to procedure.

Venous Thromboembolism Prophylaxis

This should be performed as per local guidelines. Compression stockings as a minimum.

Antibiotic regimen

- d) CIPROFLOXICIN 500MG twice daily with the first dose given the evening prior to the combined biopsy and then to be continued for 5 days.
- e) AMIKACIN or GENTAMICIN (if local microbiology guidelines prevent use of amikacin) on induction.

- f) METRONIDAZOLE 1g suppository to be given immediately after TRUS guided biopsies.

Catheterise the patient with a 16Ch or 14Ch catheter under sterile conditions (figure 1)



Figure 1. Equipment for catheterising

1. Template Mapping Biopsies

Preparation of the template grid:

- xiii. Prepare the ultrasound probe. Place a small amount of ultrasonic gel into Endocavity balloon
- xiv. Slide **Endocavity balloon** over probe and inflate balloon with water from a 50ml luer-lock syringe. Remove all air bubbles. Ensure the images are clear and without artefacts on both axial and sagittal views.
- xv. Mount ultrasound probe onto stepper platform.
- xvi. Patient in lithotomy position.
- xvii. Place urethral catheter 14Ch or 16Ch and spigot outflow.
- xviii. Lift scrotum and fix with adhesive dressing.
- xix. Clean perineum with chlorhexidine 2%.
- xx. Inject 20ml Bupivacaine + Adrenaline injection BP 0.5% w/v, 1 in 200,000 to perineal skin.
- xxi. Place **stepper** mounted ultrasound probe into rectum.
- xxii. Use sterile **Accucare drape or suitable alternative** to cover stepper and probe.
- xxiii. Use **DISPOSABLE Template Grid** (See figure 2 below) (Accucare or suitable alternative) (5mm spaced, 17G holes) with upper case letters facing the operator.



Figure 2 a and b: Disposable Template Grid

- xxiv. Align prostate so that urethra is on 'D' and ensure that the whole prostate is covered with the sampling grid-holes. Ensure that the full length of the prostate fits into the sagittal view with ultrasound probe fully inserted. 'Run-through' prostate with axial views to ensure prostate is positioned with midline on urethra and whole prostate covered by grid. If pubic arch prevents biopsy of lateral and anterior areas, the legs can be raised and the ultrasound probe repositioned.
- xxv. Obtain an ultrasound 3D Radio-Frequency volume data-file (in those centres in which this is available).
- xxvi. Biopsy protocol (please see page 8).

NB: at this point make a judgement as to whether the prostate can be fully biopsied using the Template Mapping Biopsy procedure. The main reason why Template Mapping Biopsies may not be of sufficient quality is due to prostate size and/or dimensions:

- i. if the anterior and lateral parts of the gland lie behind the pubic arch and raising and hyper-extending the legs still does not allow full gland sampling.
- ii. if median lobe is large, preventing adequate sampling.
- iii. if sagittal length of prostate is too long to allow adequate sampling with two throws of the needle (apical and basal).

If a judgement is made that template biopsies will be inadequate then only a standard set of TRUS biopsies should be carried out.

After the procedure, the patient should be informed that only a standard set of TRUS biopsies could be performed and as a result they have been partially withdrawn from the study.

Under no circumstances can the MR-imaging be un-blinded.

Preparation of material

Place white cassettes in the order of zones, 1-20 (figure 3a). Label each cassette. Have India ink ready. An orange small gauge needle should be used to pipette the ink onto the cores (figure 3b).

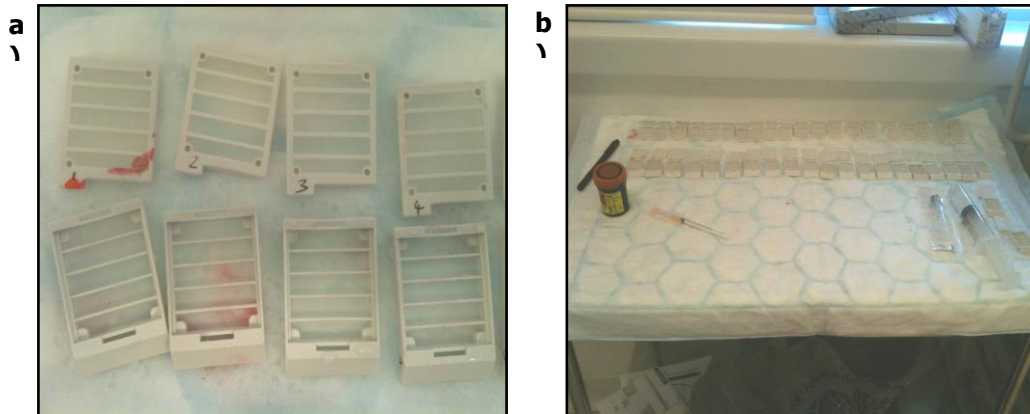


Figure 3 a and b: Cassette preparation

Line up all formalin pots ready to accept the multiwell cassettes (figure 4).



Figure 4: Formalin pots ready for cassettes

Cut approximately 4cm by 4cm strips of blue/green sterile theatre drapes (figure 5 a and b) – about 36 of these strips will be needed per case. Each should be labelled with the zone number and column letter to avoid mix-up – the end that is inked should be the apical end so that cores can be placed on the strips orientated for subsequent inking. Label the sheets with the Barzell zones. Two of each zone may be needed so prepare two lots (figure 5c).

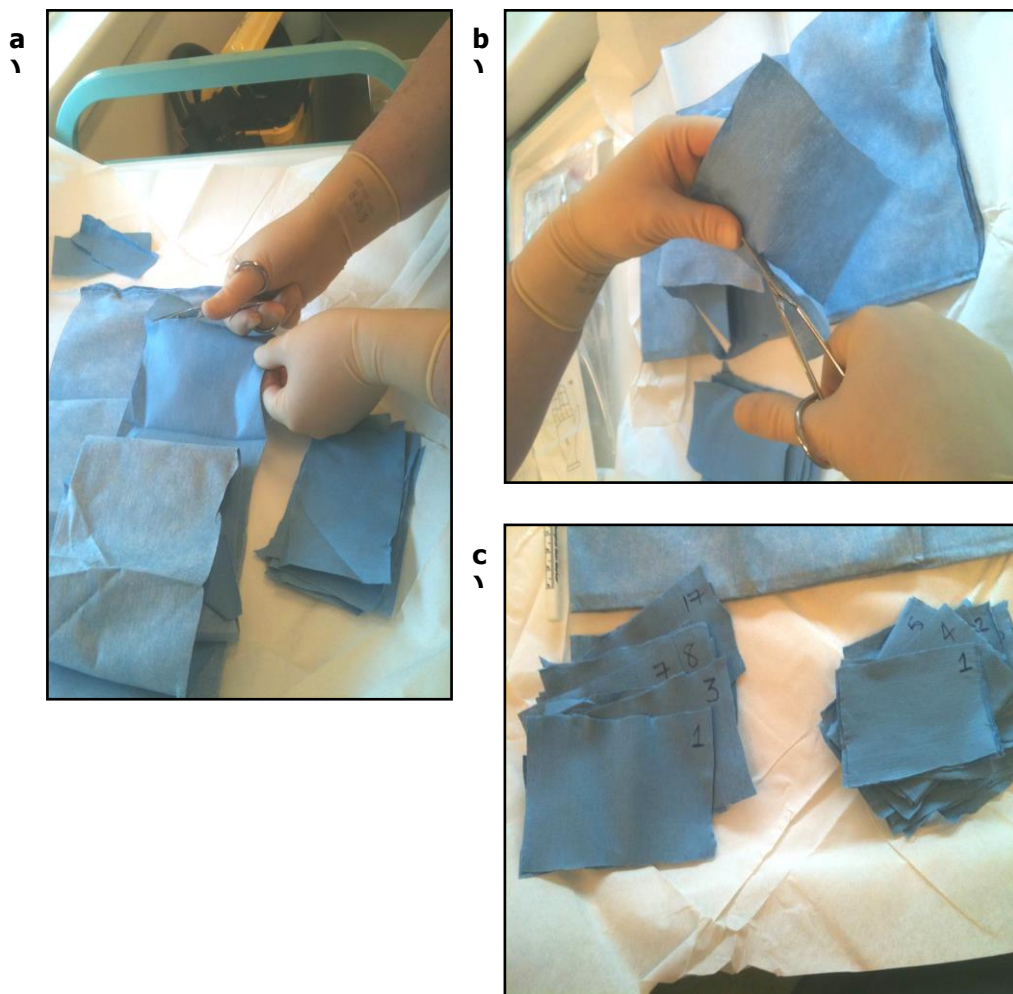


Figure 5 a-c: Preparation of sterile theatre drapes for cores

TPM Biopsy Protocol

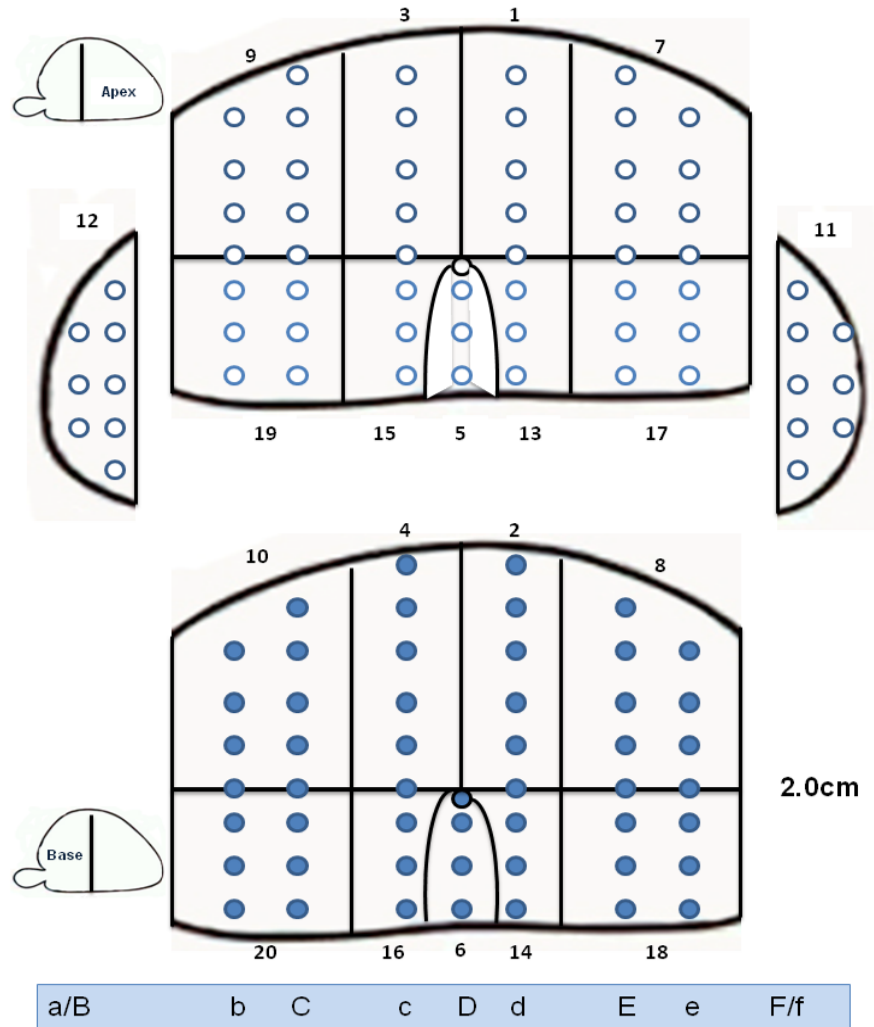
The scrub nurse should prepare the following items (figure 6)



Figure 6: Preparation of equipment prior to biopsy

List:

The



Modified Barzell Zone system should be used (please see figure 7 below) and a PROMIS TPM proforma should be completed (see appendix 1).

- | | |
|------------------------------------|--------------------------------------|
| 1 Left Parasagittal Anterior Apex | 11 Left Lateral |
| 2 Left Parasagittal Anterior Base | 12 Right Lateral |
| 3 Right Parasagittal Anterior Apex | 13 Left Parasagittal Posterior Apex |
| 4 Right Parasagittal Anterior Base | 14 Left Parasagittal Posterior Base |
| 5 Midline Apex | 15 Right Parasagittal Posterior Apex |
| 6 Midline Base | 16 Right Parasagittal Posterior Base |
| 7 Left Medial Anterior Apex | 17 Left Medial Posterior Apex |
| 8 Left Medial Anterior Base | 18 Left Medial Posterior Base |
| 9 Right Medial Anterior Apex | 19 Right Medial Posterior Apex |
| 10 Right Medial Anterior Base | 20 Right Medial Posterior Base |

Figure 7: Modified Barzell Zone System

Biopsies are to be taken in a zonal fashion but each biopsy core should be inked at the apical end and identified separately by placing a core per well in the multi-well cassettes. Start with zones 1 and 2 and take cores from the lowest coordinate in that zone and continue upwards until there is no more prostate tissue to sample. If the z axis is short then the operator needs to make a decision as to whether the core should be in the apical (e.g., zone 1) or basal pot (e.g., zone 2). Continue in this fashion for all zones except zones 11 and 12 which should be sampled one at a time.

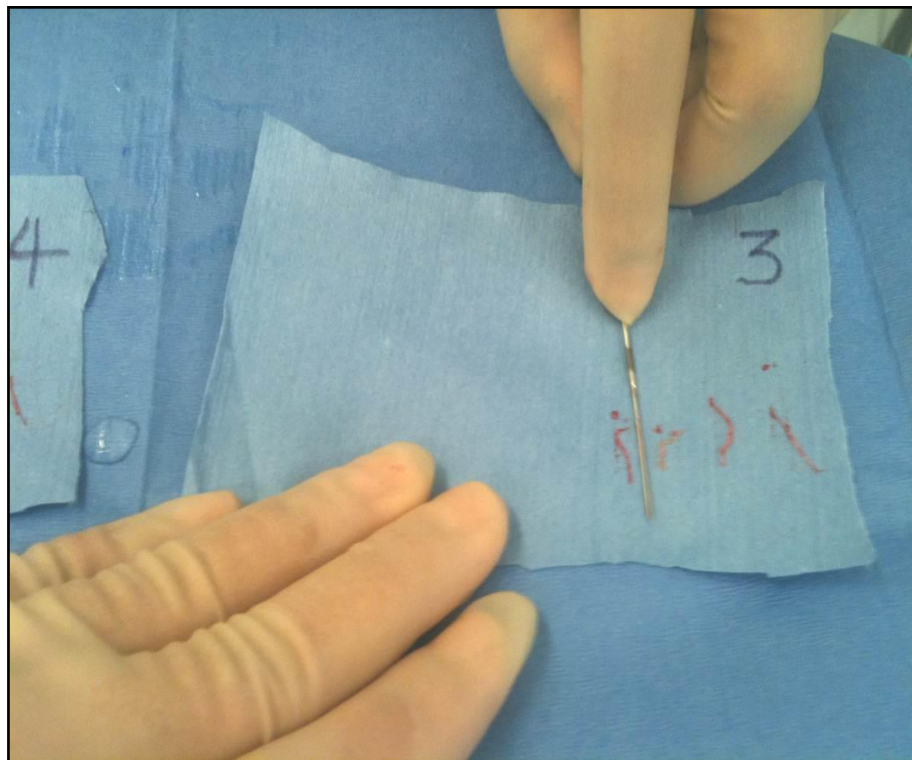
The following scheme should be used to pot the biopsies:

Labelling of cassettes

- The side of cassettes should identify the zone number only
- **Please leave the sloping edge of each cassette blank.**
- The lowest row coordinate should be potted in the well closest to the non-sloping edge.

Placing cores into cassettes

- To place cores onto strip, roll core onto paper from left to right. Place each core in order as shown below.



F

figure 8: Preparing cores prior to placing them in cassette

- Once all cores for that zone are placed on the strip, hand to assistant.
- Using fine forceps or fine gauge needles, lift and place cores into multiwell cassettes (which should have been pre-moistened (figure 9)).

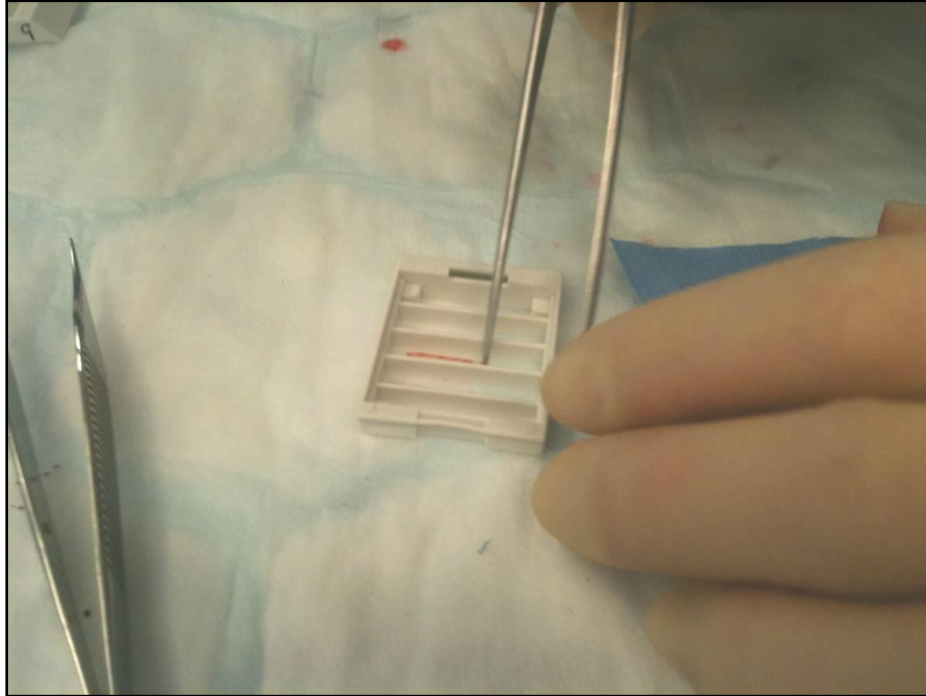


Figure 9: Placing cores into cassette

- Ink the apical end with India ink with the orange needle. Only apply a small amount.



Figure 10: Inking the apical end of core

- Ensure that cassettes go straight into Formalin containers and do not dry out (figure 11 a and b).

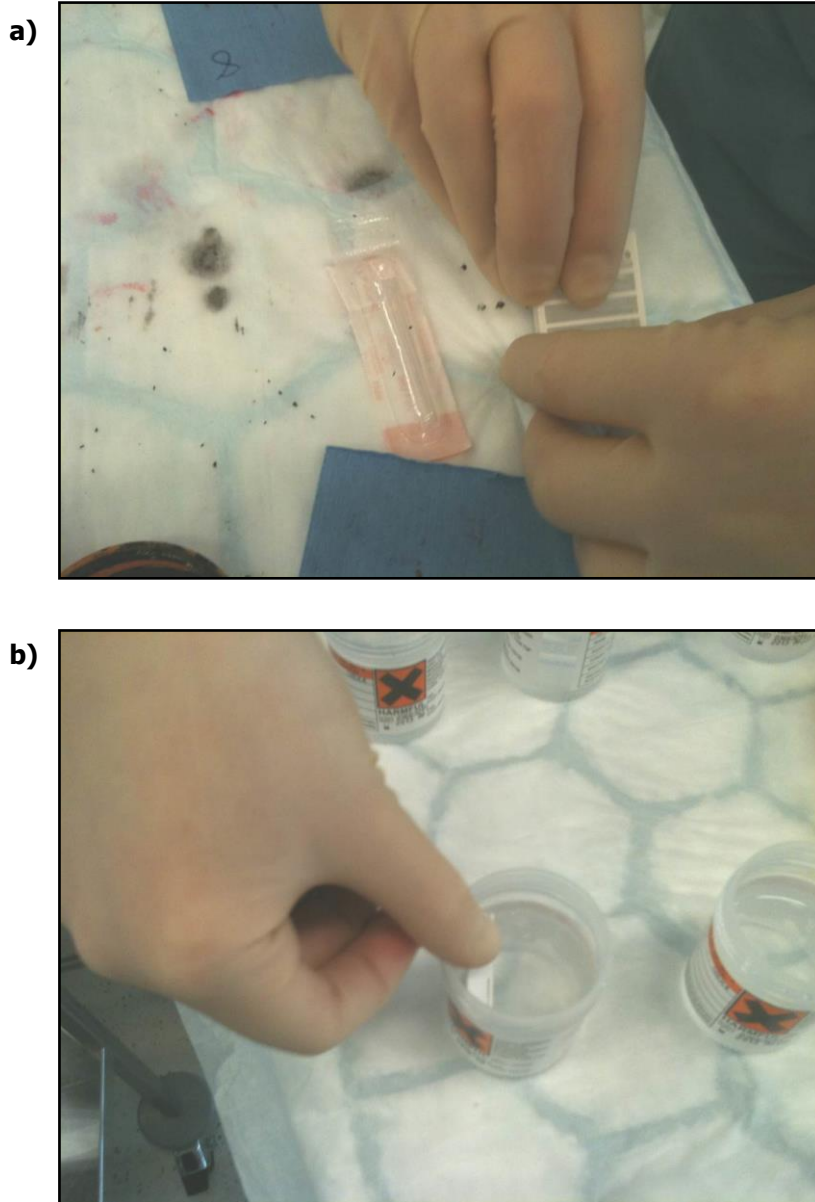
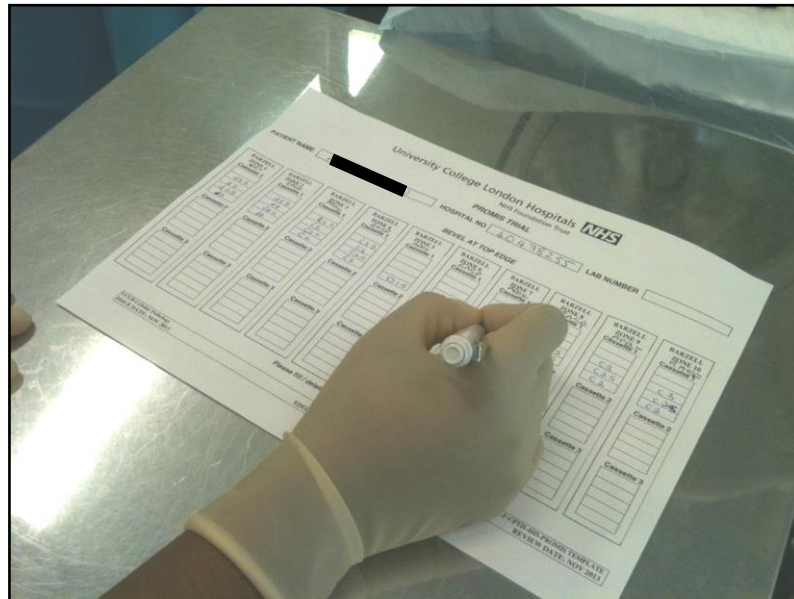


Figure 11 a and b: Place cassettes into Formalin

- More than one multiwell cassette can go into one pot but ensure that pots are labelled by Barzell zone only.
- Fill out the Pathology TPM proforma (appendix 1, figure 12 a and b)) so that an accurate record can be kept of the locations of the biopsies.

a)



b)

BEVEL AT TOP EDGE						
BARZELL ZONE 1 H&E	BARZELL ZONE 2 H&E	BARZELL ZONE 3 H&E	BARZELL ZONE 4 H&E	BARZELL ZONE 5 H&E	BARZELL ZONE 6 H&E	BARZELL ZONE 7 H&E
Cassette 1	Cassette 1	Cassette 1	Cassette 1	Cassette 1	Cassette 1	Cassette 1
d3.5	d3.5	c3.5	c3.5			
d3	d3	c3	c3			
d2.5	d2.5	c2.5	c2.5			
d2	d2	c2	c2	D1.5	D1.5	
Cassette 2	Cassette 2	Cassette 2	Cassette 2	Cassette 2	Cassette 2	Cassette 2
Cassette 3	Cassette 3	Cassette 3	Cassette 3	Cassette 3	Cassette 3	Cassette 3

Please fill / delete as appropriate

UCLH-Cellular Pathology
ISSUE DATE: NOV 2014

Figure 12 a and b: Enter core location and cassette number onto TPM proforma

After Template Mapping biopsies are complete, apply blue gauze pressure dressing with appropriate adhesive tape. This can be removed after a day.

3. Transrectal Ultrasound Guided Biopsies

- j) Place patient in left lateral position.
- k) Using a rolled up swab soaked in chlorhexidine 2% insert into rectum to clean. Repeat 2 or 3 times.
- l) Using a needle mount on the probe, standard 10-12 core trans rectal biopsies are taken using the following protocol. Each biopsy is to be identified separately and a TRUS proforma should be used (see appendix 2).
 - A: Right lateral base
 - B: Right lateral mid
 - C: Right lateral apex
 - D: Right parasagittal base
 - E: Right parasagittal mid
 - F: Right parasagittal apex
 - G: Left lateral base
 - H: Left lateral mid
 - I: Left lateral apex
 - J: Left parasagittal base
 - K: left parasagittal mid
 - L: Left parasagittal apex
- m) Each core should be identified individually
- n) Place cores into multi-well cassettes with right and left identified separately. Ensure the multiwell cassettes are appropriately labelled with the biopsy location letter (as shown in figure 13 below)
- o) Inking the core is not necessary.
- p) If 10 cores are taken then only two multiwell cassettes are needed.
- q) If 12 cores are taken then 4 multiwell cassettes are needed.
- r) Ensure urine is clear by opening catheter. If not, bladder washouts should be carried out until clear and/or a 20Ch-22Ch 3-way irrigating catheter left in with irrigation for 1-2 hours in recovery. Catheter should be removed prior to returning to ward if irrigation is clear. This is at the operator's discretion.

Example of Right side

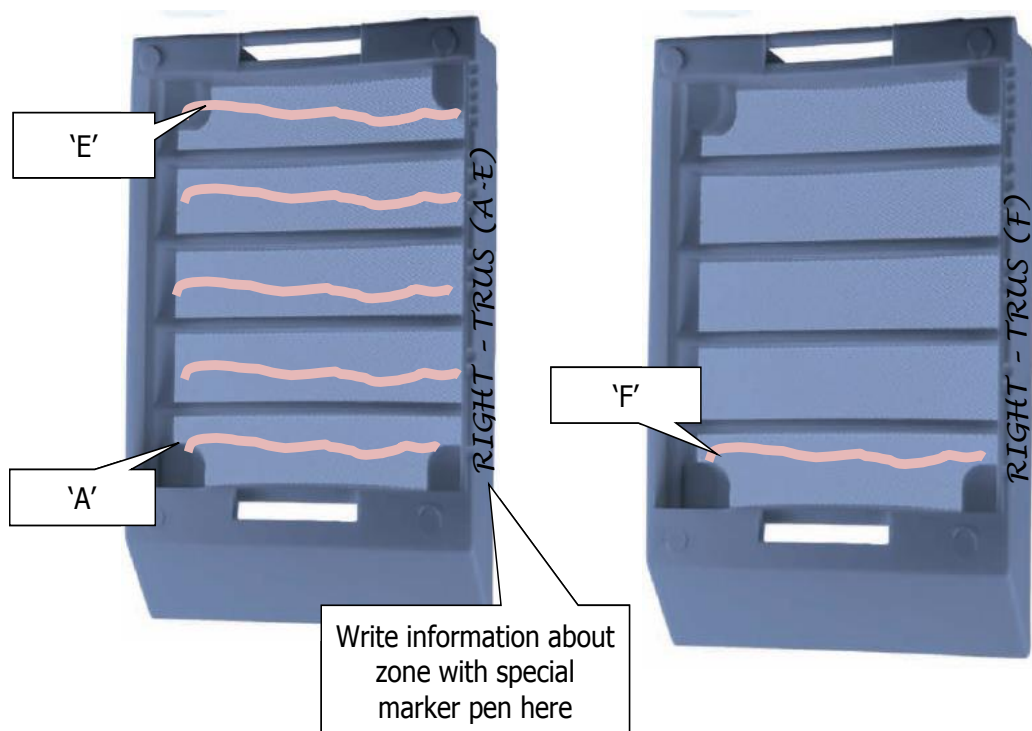


Figure 13: Potting TRUS biopsy cores into multi-well cassette

Labelling and sending biopsy samples from Template Mapping and TRUS to histopathology

- c) Template mapping: Histopathology request forms should identify patient as a member of PROMIS, the PROMIS patient ID should be written in the section 'what information are you looking for from this biopsy?' or equivalent section on your local pathology request form. All multi-well cassettes from a patient, PROMIS TPM proforma and histology request form should be packaged together and clearly labelled using your standard patient sample labels.
- d) TRUS: Histopathology request forms should identify patient as a member of PROMIS, the PROMIS patient ID should be written in the section 'what information are you looking for from this biopsy?' or equivalent section on your local pathology request form. All pots, PROMIS biopsy proforma and histology request forms should be packaged together and clearly labelled using your standard patient sample labels.
- e) All pathology should be transported by medical courier to University College London Hospitals NHS Trust Histopathology Department. Addressed to: Dr Alex Freeman, Consultant Histopathologist. Department of histopathology, 3rd/4th floor, Rockefeller Building, 21 University Street, WC1E 6BT

Processing of Biopsy samples at the Central UCLH laboratory

- g) On arrival, the UCLH pathology laboratory must process the Template Mapping Biopsies and TRUS guided biopsies separately.
- h) Template Mapping Biopsies should be assigned to one of the two trial pathologists (Dr Charles Jameson or Dr Alex Freeman) for reporting. TRUS biopsies should be assigned to the other.
- i) There should be no communication with respect to a patient between the two reporting pathologists. In the case of uncertainty over an area on histology the third named pathologist should be consulted.
- j) The reporting proforma for the pathology of each core will identify:
 - Location
 - Length of core (mm)
 - Presence of cancer (Yes/No)
 - Location of cancer (apex, mid, base thirds of core)
 - Primary Gleason grade (if cancer present)
 - Secondary Gleason grade (if cancer present)
 - Tertiary Gleason grade (if cancer present)
 - Amount of cancer (UK and ISUP) (mm)
 - Presence of severe inflammation (Yes/No)
 - Presence of HGPIN (if no cancer) (Yes/No)
- k) Information on cores will be recorded electronically in the MRC CTU electronic Macro database system.
- l) See the PROMIS reporting results to patients SOP for information on retrieving results.

Patient's Initials:

Date of TPM Biopsy:

PATIENT NAME	HOSPITAL NO	LAB NUMBER
<div style="display: flex; justify-content: space-between;"> <div> BARZELL ZONE 1 APEX </div> <div> BARZELL ZONE 2 BASE </div> <div> BARZELL ZONE 3 APEX </div> <div> BARZELL ZONE 4 BASE </div> <div> BARZELL ZONE 5 APEX </div> <div> BARZELL ZONE 6 BASE </div> <div> BARZELL ZONE 7 APEX </div> <div> BARZELL ZONE 8 BASE </div> <div> BARZELL ZONE 9 APEX </div> <div> BARZELL ZONE 10 BASE </div> </div>		

TPM Proforma dv0.0 24 Jan 2012

Appendix 2 TRUS Proforma

Uni

[Insert local header]

PROMIS Trial Number:

IVUS FOUR

Date of Birth:

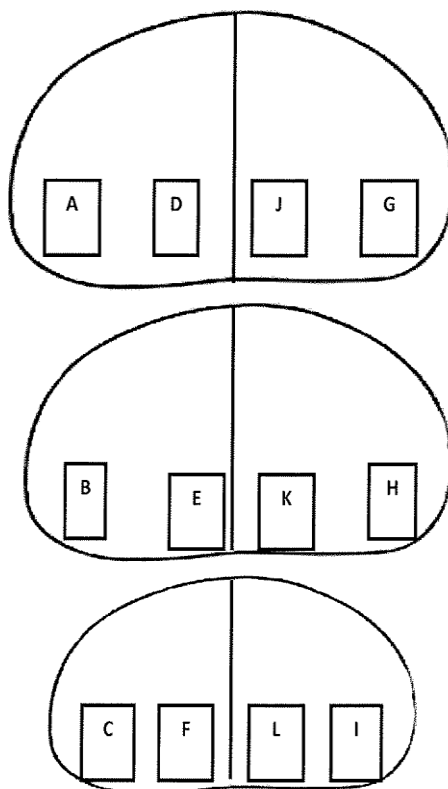
Date of TRUS Biopsy:

Patient's Initials:

PATIENT NAME

HOSPITAL NO

LAB NUMBER



A = Right lateral base ☐

G = Left lateral base ☐

B = Right lateral mid ☐

H = Left lateral mid ☐

C = Right lateral apex ☐

I = Left lateral apex ☐

D = Right para base ☐

J = Left para base ☐

E = Right para mid ☐

K = Left para mid ☐

F = Right para apex ☐

L = Left para apex ☐

TRUS Proforma dv0.0 24 Jan 2012

14.3.2. Mp-Mri



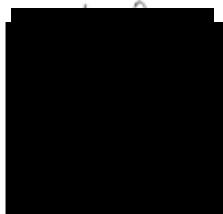
Developed with the NCRI Prostate Clinical Studies Group
Part of the NIHR National Cancer Research Network Portfolio
ISRCTN Number - 16082556
UCL reference – 11/0009
REC reference – 11/LO/0185



Evaluation of multi-parametric magnetic resonance imaging in the diagnosis and characterisation of Prostate Cancer

MP-MRI Standard Operating Procedures

v02.00 18th September 2013

Author		
Alex Kirkham Lead Radiologist	Signature	Date:
Reviewed and Authorised by		
Hashim Ahmed Co-Chief Investigator	Signature: 	Date: 20/10/2013

Revision History

Version	Author	Date	Reason for Revision
1.00 – 2.00	Louise Brown, Alex Kirkham & Cybil Adusei	17/01/2013 – 18/09/2013	<ul style="list-style-type: none"> - More explicit description of methods for ensuring MRI reports remain blinded to other investigators. - Additional guidance on staging disease. - Guidance on what to do if sequences are missed. - Information on IXICO and their role. <p>Importance of MRI being reported and submitted before biopsy highlighted and justification given.</p> <ul style="list-style-type: none"> - Clear guidance on sector scoring scheme and variables for the primary outcome. - ESUR 2012 guidelines inserted

1. These specifications are a set of minimum requirements. The study has been designed to allow technical developments to be incorporated into the scanning protocol as they occur.
2. There will be an external process for quality control. It is envisaged that scans will be checked within 48 hours, to enable rescanning if necessary before biopsy. In instances where it is necessary to raise a query regarding the dataset there may be a slight delay.
3. The sequences will be distributed to participating centres as a Siemens 'Phoenix' file. Any deviation from the established protocol should be discussed with the lead radiologist.
4. Factors meaning exclusion from the study:
 1. a) eGFR $<50\text{ml/min/1.73m}^2$ (intravenous (IV) contrast cannot be given)
 2. b) Standard contraindications to MRI
 3. c) Metallic hip replacement or extensive pelvic orthopaedic metalwork likely to degrade diffusion and contrast-enhanced sequences.

1. MRI Procedure

Details of the scan parameters are given in Appendix 1. These are a *minimum* set of requirements: additional sequences (e.g. 3D isotropic T2 sequences, diffusion tensor imaging, additional ADC maps) are permitted. In addition, improvements in resolution (smaller voxel size or slice width and improved time resolution on the dynamic sequences) can be incorporated after discussion with the lead radiologist.

- a) A standard safety questionnaire should be completed.
- b) For patients undergoing contrast enhancement: set up IV line in a vein in the antecubital fossa, connected to an automated injector with two syringes (contrast and 20ml saline flush). Contrast and flush should be given at 3ml/s.
- c) 20mg buscopan or 1mg glucagon IV to be given just before the start of the scan.
- d) T2 sequences:

Small field of view in 3 planes. The fields of view provided on the standard sequences are enough to cover most prostates. However, if the tips of seminal vesicles and the external sphincter cannot be included on the axial sequence, then the number of slices (and with it the scan time) should be increased. In all cases the slice width should remain at 3mm, with a 10% interslice gap. For diagrams of coverage, see Appendix 2 of this document.

- e) Diffusion sequences:

Two sets of sequences are the minimum requirements for the diffusion data. Individual centres are free to do additional sequences (eg for anisotropy).

- i) Multi-b with b values of 0,100,500 and 1000 s/mm². 16 averages using a 3 trace technique. Standard Siemens algorithm for determination of ADC (currently includes b0 with monoexponential decay fitting, but this may be revised)
- ii) b1400 s/mm² with 32 averages. The b value can be higher at 3T (usually 2000). See Appendix 1 for the detailed parameters.

- f) VIBE sequences:

- i) The multi-flip angle VIBE sequence is a relatively quick method for the quantitative determination of T1 relaxation. It is not essential for PROMIS but should be included if possible. Coverage should be the same as for the dynamic contrast enhanced sequences, and includes the external sphincter and seminal vesicles as for the T2 axial sequences. If this cannot be ensured, the priority is to include the prostatic apex: the seminal vesicle tips are less important, as long as most of the vesicles are included. Alternative methods of quantifying T1 may be incorporated later.

ii) Dynamic contrast enhancement. Contrast is 0.1mmol/kg of low molecular weight gadolinium-based contrast: Magnevist or Dotarem (preferred in those with mild renal impairment), given at 3ml/s. This should be followed by a flush of 20ml Normal Saline. The infusion is started concurrently with the third dynamic acquisition. Acquisitions are continued for at least 5 minutes 30 seconds after the start of the contrast infusion.

g) The performing radiographers will complete a subject data form for forwarding with the DICOM file to the Imaging contract research organisation (IXICO). This will include the PROMIS Trial ID and date of birth as well as a description of any particular problems or comments arising during the scan. Details such as the dose of contrast used and patient weight should be entered into trial tracker.

Note: If a patient is not scanned using all three sequences in error they must be re-scanned using all sequences at a later date. It is not acceptable to scan the patient on a different day using the sequences that were missed.

2. Quality Control (QC) & Quality Assurance (QA)

Quality Control (QC)

Performed by IXICO who are an external imaging contract research organisation (CRO).

Each imaging dataset will be specifically checked for the following:

- i) That the dataset acquired is complete
- ii) Images must cover anatomy of interest and be free of significant artefacts
- iii) Slice positions/thickness/plane of imaging/FOV of the images correspond to the imaging protocol
- iv) Recorded patient weight and injected Gd-DTPA dose volume will be checked for consistency
- v) Evidence of and notes regarding untoward events during the dynamic acquisition, e.g., movement, coughing, , poor injection technique,
- vi) FOV, offset, slice level/thickness, receiver gain and image scaling factors of the dynamic sequence and multi-flip angle images should be consistent with each other during the DCE-MRI study

All scans will be assessed within 48 hours, to allow referral to the supervising radiologists for consideration of rescanning, if necessary. Where biopsy is planned less than 48h after the MRI the QC company should be notified that an urgent check is required.

Following completion of the QC, a report will be sent to both the local and central radiologists.

Quality Assurance (QA)

Standard manufacturer's service summaries during the study should be sent to the CRO. In addition, a localphantom will be used for the diffusion MRI scans.

There will be regular QA measurements according to the following schedule:

- Before beginning and end of the study
- At least yearly

Events necessitating further QC with phantoms include: untoward events that may affect scanner performance, quenches and following software upgrades.

3. MRI reporting

a) In all cases, the MRI must be reported before the prostate biopsy takes place. This is important for the following reasons:

- 1) The quality of the MRI can be checked to ensure a repeat scan is not required prior to the CPB.
- 2) The ascertainment of any patients with T4 disease should have happened before the CPB so that they can be withdrawn and have their care accelerated outside of the study.
- 3) The withdrawal of any patients with >100cc glands. This prevents these patients from a) having an unnecessary general anaesthetic and b) means they do not get booked into an unnecessary theatre slot for a CPB that will not be performed.

b) The MRI DICOM files will be stored on a central server and downloaded onto a local, certified DICOM reader. The default reader will be OSIRIX on a mac workstation.

c) MP-MRI CRF reports will be scanned (at least 300dpi) and emailed to MRC CTU (clinical trials unit). Local and central radiologists must report separately and must not be able to refer to each other's MP-MRI CRFs. The local computerised hospital results system and PACS system must not be uploaded with the results of the MRI reports until notification from the MRC CTU has been received that all biopsy results have been completed. Hard copies of the MRI CRF will be kept in a secure file next to the reporting workstation in each centre. Each radiologist will have their own file accessed by lock and key, such that access to the reports can only be granted by the radiologist who reported the MRI.

d) All volumes should be measured by planimetry using a dedicated ROI volume measurement tool.

e) The MP-MRI CRF (given in Appendix 3) has 4 components

1) Size of prostate

2) A sector scoring scheme.

It is very important that this is reported strictly in order: T2 sequences only, T2+diffusion, and T2+diffusion+dynamic contrast. It is also very important that once the radiologist has moved on to the next stage of these 3 sequences, they cannot go

back and alter any of the scores. The scores on the grid are for the presence of *UCL definition 2 disease* (Gleason 3+4 or >0.2cc) The boxes below the grid are for the radiologist to score the overall likelihood of tumour in the whole prostate, firstly for any tumour, and then for two definitions of significant disease and finally the presence of dominant Gleason 4 tumour. These boxes are divided into 'right,', 'left' and 'overall'. The scores for each level of significance may be the same, or may diverge: it should be possible (though rare) to score 4/5 for any disease, 3/5 for definition 2 disease and 2/5 for definition 1 disease. If this is not clear (it is a new way of reporting for most of us), please discuss with the lead radiologist. Please note that it is the overall score for UCL definition 2 (Gleason 3+4) that will be used in the primary analysis.

3a) Draw the lesion on the 27 sector model of the prostate. Each region corresponds to 1/3 of the prostate. Label lesions from 1 to 6 (the 6 largest lesions only should be included). Pay particular attention to placement within anatomical zones (e.g. transition zone). Diffuse change scoring 3/5 or more *must* be marked on the diagram, although a volume measurement is not necessary if the majority of the peripheral zone is involved. It should also be given a number, and included in the 'numerical scoring per lesion' section below.

3b) Numerical scoring *per lesion*. The scores for T2, diffusion and contrast are collected to give an idea of the individual performance of each MRI parameter. They should be derived in strict accordance with the ESUR 2012 prostate MRI guidelines (see appendix 5). This is so that we can help to validate their semi-objective criteria. The overall score for each lesion, on the other hand, is a *subjective* assessment of the likelihood of disease, and not just the average of the individual sequence scores (see Barentsz et al Eur Radiol (2012) 22:746–757). In addition the following data will be collected per lesion:

- Template co-ordinates: the two most likely template grid locations to be positive for each lesion. Spacing on the template is 5mm, and line 1 lies just inside (1-3mm) the posterior capsule at its most posterior point. Appendix 4 contains a picture of the template grid.
- Curve shape: plot curve (again, with an oval entirely within enhancing lesion). This can be plotted on Siemens Leonardo workstations (mean curve or tissue 4D tools) or with the OSIRIX ROI Tools / ROI enhancement plugin

- ADC value. Measured by placing an *ova*/ ROI entirely within the lesion, on the most conspicuous slice, avoiding edge pixels but covering as much of the lesion as possible.
- Zone: Peripheral, transitional, central or combination.
- Maximum diameter: on any sequence.
- Volume: measure on the T2 sequence, as long as the lesion is seen. If the lesion is not well seen on T2, use diffusion or contrast (whichever is clearest). Volume is not a primary outcome variable, and we will not have radical prostatectomy for correlation in most cases. If there is diffuse change involving the majority of the peripheral zone, put 'diffuse' instead of measuring volume.
- Distance from posterior capsule. The position to measure on the posterior capsule can be determined by imagining an ultrasound probe in the rectum against the prostate: how far must the needle travel from the capsule to reach the tumour?
- Estimated Gleason grade: this is a *purely subjective* score based on your experience (note that the literature shows an inverse correlation between ADC and Gleason score). What matters is that the reporters are consistent in their own attribution. The data may later be dichotomised.

4) Staging. Each of the staging scores is graded in the same way as the presence of disease, from 1-5. Note that these scores are not for the *degree* of extracapsular extension or seminal vesicle involvement. Rather, they are an assessment of the probability that such extension is present. If lymph node involvement is suspected, give maximum *short axis* lymph node diameter and its location.

For safety purposes a score of 4 or 5 for Sphincter, Rectum or Nodes indicates that the patient had T4 stage disease and they should be immediately withdrawn from the study. Patients found to have prostate volume of 100cc or more should also be immediately withdrawn from the study. The radiologist must contact the MRC CTU office to let them know the patient has T4 disease or ≥ 100 cc prostate volume and that the results of the MP-MRI should be unblinded and the patient withdrawn from the study.

f) A note on the scoring of 'any disease':

We know that statistically some tumour is more likely than not to be present in some of the patients scanned, whether visible on MRI or not (for example a 78y man with a PSA

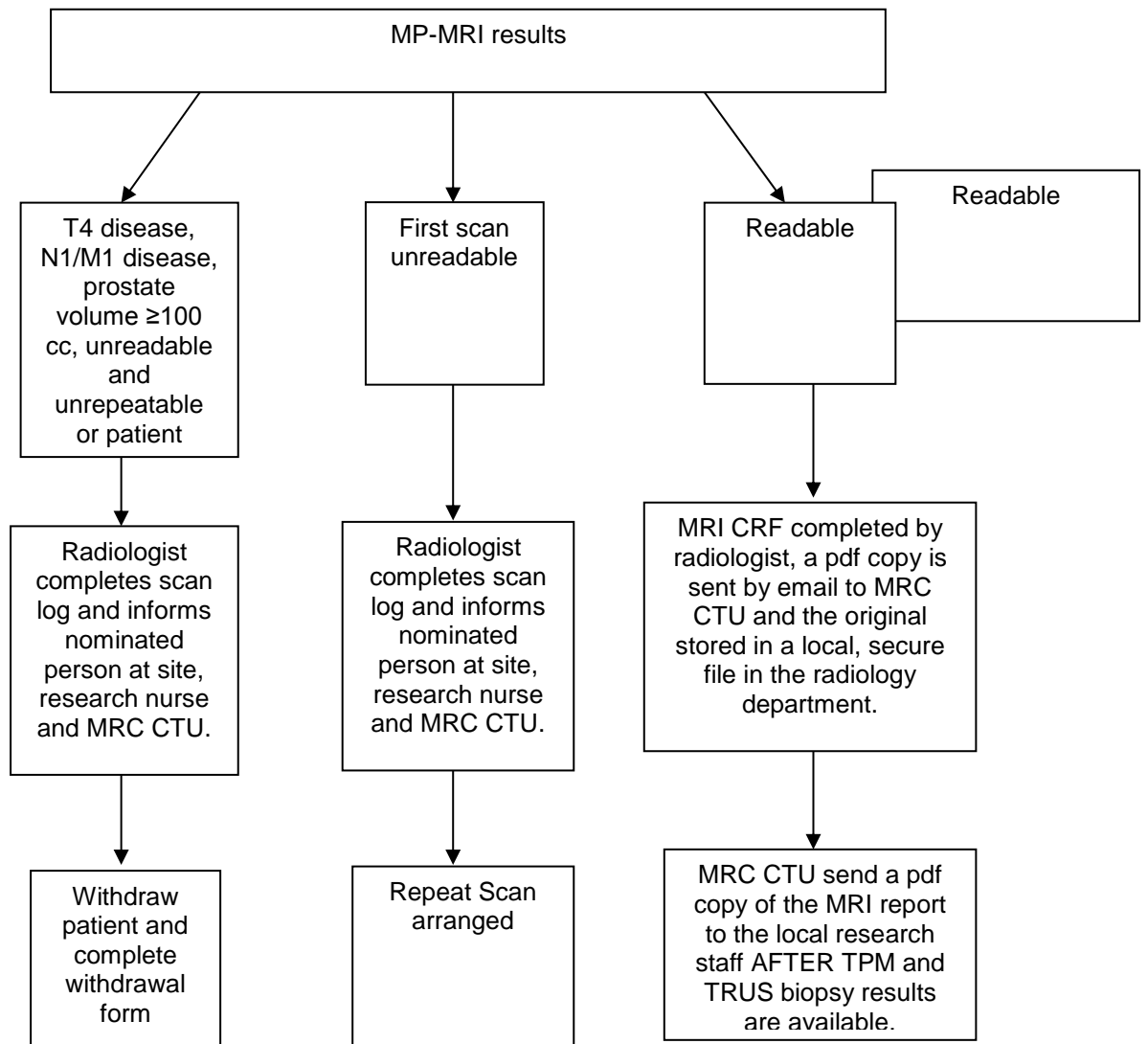
of 10). It may therefore seem sensible to score 3/5 or more in almost all such cases as an overall score for any disease. This should be avoided, and two points in particular should be considered:

- i) It is accepted that MRI will not detect very small amounts of low grade disease. It is not the aim of this study to predict such disease: rather, we are aiming to identify visible tumour.
- ii) Diffuse, smooth enhancement or T2 change that may obscure low grade tumour is always a problem for the reporting radiologist who is trying to avoid 'equivocal' scores of 3/5 where possible. Although the diffusion sequences show most bulky tumours, they usually do not show small patches of 3+3 tumour. In general, heterogeneous patches of T2 change are more likely to represent tumour than those which are smooth (or stranded), and symmetrical. Smooth, symmetrical change is particularly common in relatively young men, where it usually does not represent tumour. It is also dependent on the scanning technique (and magnet strength). For this reason all PROMIS radiologists will take part in training days where many instances of diffuse change will be discussed.

4. Unreadable/Unrepeatable scans

If the MRI scan was unreadable, this will be identified in the quality control review performed by IXICO. The nominated staff member should make another appointment for a repeat MRI as soon as possible, if the patient consents to this. If a patient's first scan is unreadable and they subsequently refuse a second scan, they will be withdrawn from the trial. A Withdrawal form should be completed. Patients registered into PROMIS but for whom there is no subsequent MP-MRI result (for any reason) should be withdrawn from the study and any remaining procedures. A withdrawal form should be completed if this occurs and it should be sent to the MRC CTU.

Management of MP-MRI scans



Appendix 1

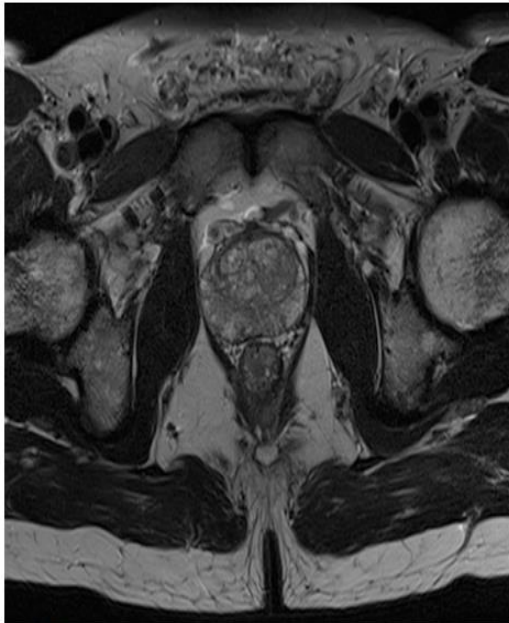
Detailed scan parameters. Please note that a Phoenix disc will be provided for all centres.

	TR	TE	Flip angle/degrees	Plane	Slice thickness (gap)	Matrix size	Field of view /mm	Time for scan
1. T2 TSE	5170	92	180	Axial, coronal, sagittal	3mm (10% gap)	256x256	180x180	3m 54s (ax)
2. VIBE at multiple flip angles for T1 calculation (optional)								Will be included in the Phoenix file
3. VIBE fat sat	5.61	2.52	15	Axial	3mm	192x192	260x260	Continue for at least 5m30s after contrast
4. Diffusion (b values: 0, 150, 500, 1000)	2200	Min (<98)		Axial	5mm	172x172	260x260	5m 44s (16 averages)
5. Diffusion (b=1400)	2200	Min (<98)		Axial	5mm	172x172	320x320	3m 39s (32 averages)

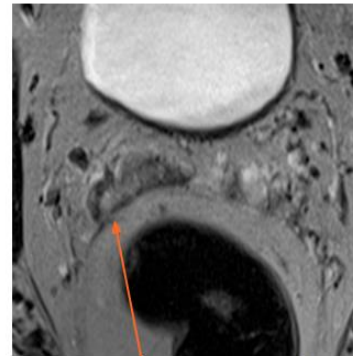
Appendix 2 - A guide to coverage for the T2 sequences

T2 axial

include external
sphincter

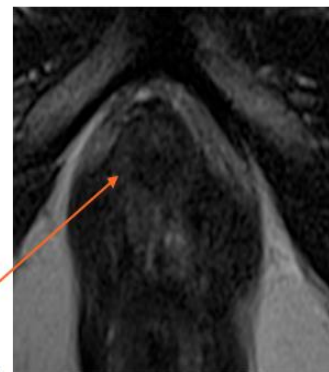


middle



try and include
seminal vesicles to
tips

base



include external
sphincter to below
apex of prostate

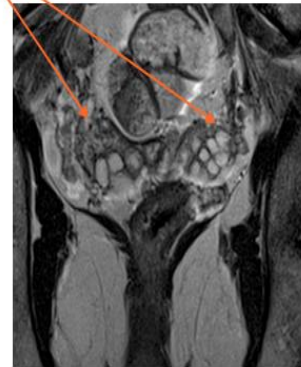
apex

T2 coronal

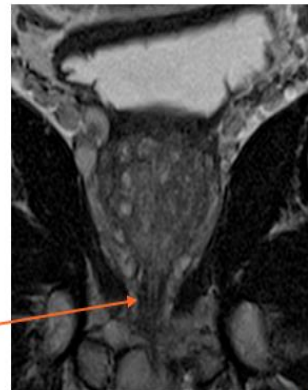
include seminal
vesicles to tips



middle

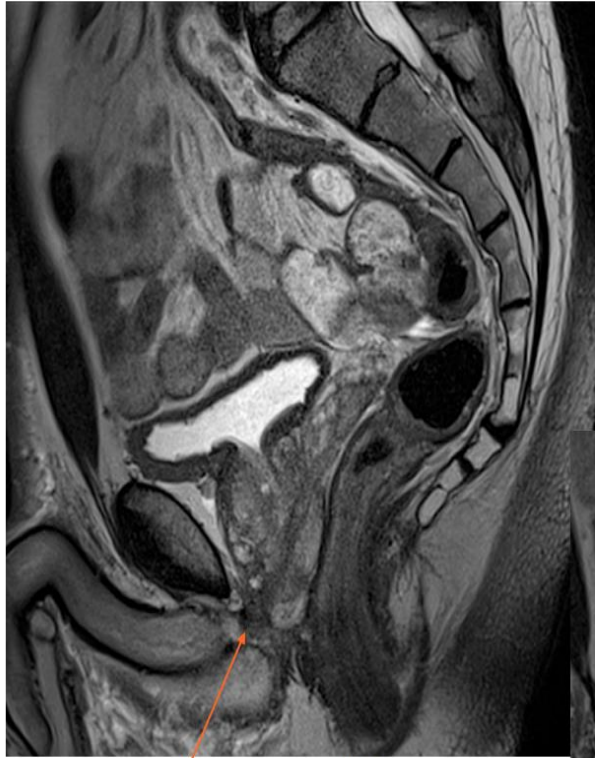


posterior



middle

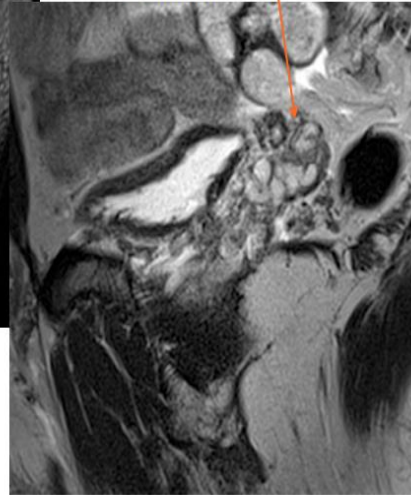
include external
sphincter



T2 sagittal

must include
seminal vesicles to
tips

off midline



must include
external sphincter

midline

Appendix 3 - MP-MRI CRF



MP-MRI - Form 2
v2.1 06th September 2013

Page 1 of 1

Patient's Initials: Date of Birth: Trial No.: Reporter: ☐ Local ☐ Central ☐ Additional ☐
Hospital Number: Scan Date: Are you blind to all results for this patient? Yes ☐ No ☐
PSA ng/ml: Tesla scanner: 1.5 ☐ OR 3.0 ☐

1. SIZE OF PROSTATE

Transverse cm Anterior-Posterior cm Cranio-Caudal cm Volume cm³

If gland volume is ≥ 100 cm³ submit this form immediately to the MRC CTU and complete a withdrawal form.

2. SECTOR (for UCL Definition Two disease) (Report strictly in order, and put a value 1-5[†] in each ROI). P = Posterior <1.7cm (measured from posterior capsule)

	T2	T2 + DW	T2 + DW + DCE
Base			
Mid			
Apex			

Risk category	Disease Threshold	MRI Score [†] (1-5)		
		R	L	Overall
Any cancer	Any Disease			
Definition Two (Primary outcome)	≥ 0.2 cc and/or $\geq 3+4$			
Definition One	≥ 0.5 cc and/or $\geq 4+3$			
Dominant Gleason 4	$\geq 4+3$			

3a. INDIVIDUAL LESIONS (Please draw and number measurable lesions on diagram below)

Base

Mid

Apex

Right Left

3b. INDIVIDUAL LESIONS

(Using the lesions drawn in 3a please score each lesion on the table below)

Lesion No.	T2	D	C	All	Curve 1=Slow rise 2=Fast 3=Early peak	ADC	Zone	Max diameter	Volume (cm ³) or 'Diffuse'	Distance from posterior capsule	Estimated Gleason Grade	Estimated Cancer Significance
	MRI Score [†] (For T2, D, C: 1-5 as on ESUR 2012 guidelines)				1-3	Value	PZ/TZ/CZ/Combination	mm		mm	e.g. 3+4	Not sign/Def 2/Def 1
1												
2												
3												
4												
5												
6												

4. STAGING

	Vesicles involved?	Extra-capsular?	Sphincter (T4)?	Rectum (T4)?	Nodes?
MRI Score [†] (1-5)					
If score >2, Left or Right?					

If score for nodes >2, max short axis nodal diameter? (mm)

[†] MRI Score
1=Highly likely benign
2=Likely benign
3=Equivocal
4=Likely malignant
5=Highly likely malignant

Signature:

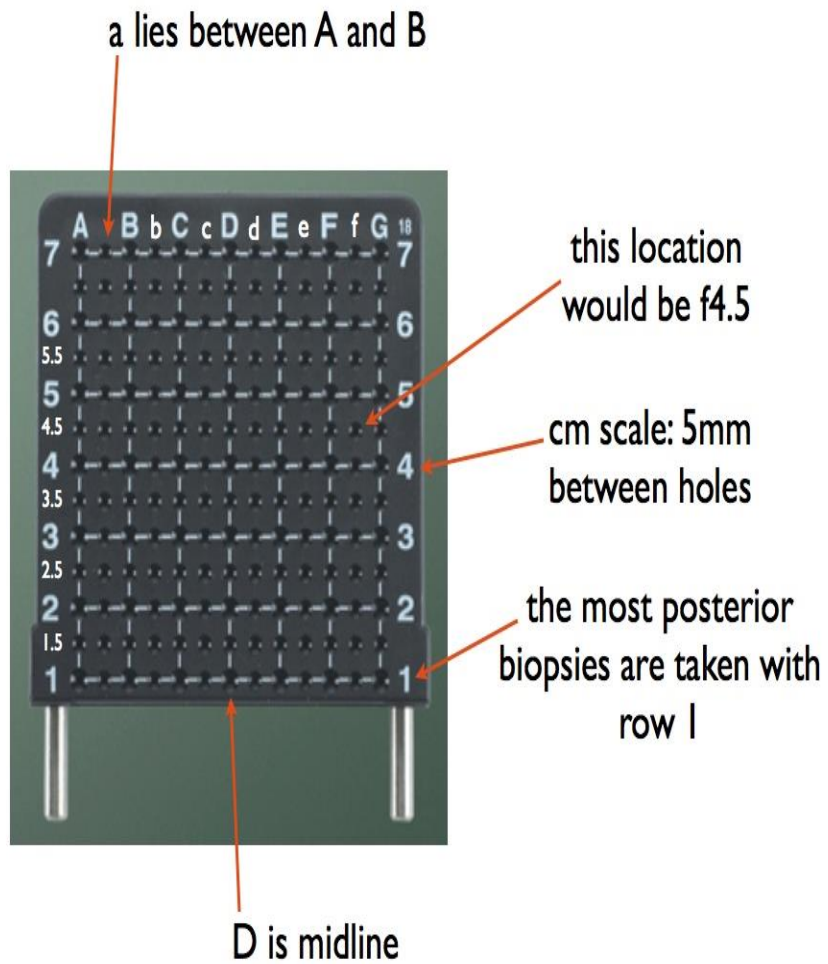
Author Name:

Report Date:

Please email a scanned copy to MRCCTU.PROMIS@ucl.ac.uk

Appendix 4

Template biopsy grid:



Appendix 5 - PI-RADS scoring system (see Eur Radiol (2012) 22:746–757)

Score Criteria

A1. T2WI for the peripheral zone (PZ)

- . 1 Uniform high signal intensity (SI)
- . 2 Linear, wedge shaped, or geographic areas of lower SI, usually not well demarcated
- . 3 Intermediate appearances not in categories 1/2 or 4/5
- . 4 Discrete, homogeneous low signal focus/mass confined to the prostate
- . 5 Discrete, homogeneous low signal intensity focus with extra-capsular extension/invasive behaviour or mass effect on the capsule (bulging), or broad (>1.5 cm) contact with the surface

A2. T2WI for the transition zone (TZ)

- . 1 Heterogeneous TZ adenoma with well-defined margins: "organised chaos"
- . 2 Areas of more homogeneous low SI, however well marginated, originating from the TZ/BPH
- . 3 Intermediate appearances not in categories 1/2 or 4/5
- . 4 Areas of more homogeneous low SI, ill defined: "erased charcoal sign"
- . 5 Same as 4, but involving the anterior fibromuscular stroma or the anterior horn of the PZ, usually lenticular or water-drop shaped.

B. Diffusion weighted imaging (DWI)

- . 1 No reduction in ADC compared with normal glandular tissue. No increase in SI on any high b-value image ($\geq b800$)
- . 2 Diffuse, hyper SI on $\geq b800$ image with low ADC; no focal features, however, linear, triangular or geographical features are allowed
- . 3 Intermediate appearances not in categories 1/2 or 4/5
- . 4 Focal area(s) of reduced ADC but iso-intense SI on high b-value images ($\geq b800$)
- . 5 Focal area/mass of hyper SI on the high b-value images ($\geq b800$) with reduced ADC

C. Dynamic contrast enhanced (DCE)-MRI

- . 1 Type 1 enhancement curve
 - . 2 Type 2 enhancement curve
 - . 3 Type 3 enhancement curve
- +1 For focal enhancing lesion with curve type 2–3+1 For asymmetric lesion or lesion at an unusual place with curve type 2–3

14.3.3. Infection and sepsis




Developed with the NCRI Prostate Clinical Studies Group
Part of the NIHR National Cancer Research Network Portfolio
ISRCTN Number - 16082556
UCL reference – 11/0009
REC reference – 11/LO/0185




Evaluation of multi-parametric magnetic resonance imaging in the diagnosis and characterisation of Prostate Cancer

Managing episodes of urinary infection and/or sepsis following the Combined Prostate Biopsy Standard Operating Procedures

dv00.02 09SEPT2013

Author		
Hashim Ahmed Co-Chief Investigator	Signature 	Date:
Reviewed and Authorised by		

Mark Emberton Chief Investigator	Signature 	Date:
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Revision History

Version	Author	Date	Reason for Revision

All Serious Adverse Events are of high importance in a clinical trial and must be reported within 24 hours of the site becoming aware of an event. These specifications are a set of minimum requirements to aid the clinical management for PROMIS patients who develop infection or sepsis, following their combined prostate biopsy (CPB) procedure. At the time of discharge, the patient is to be given a PROMIS patient card detailing the medication that was given at the time of the combined prostate biopsy (CPB). This card also gives contact details for the PROMIS research team during working hours and a link to information about the trial out-of-hours.

As part of this trial it is possible that a patient has had any of the following biopsies:

- 20 zone template prostate biopsy followed by trans rectal ultrasound biopsy
- 20 zone template prostate biopsy alone
- 20 zone limited (2-3 cores per zone) prostate biopsy alone
- Transrectal ultrasound biopsy alone

Regardless of which biopsy or biopsies the patient has had, this document should be read and the site responsible for the patient contacted.

Combined Prostate Biopsy procedure

This procedure is performed by a competent physician trained and certified according to the most recent version of the PROMIS protocol. The physician is blinded to the MR imaging and other imaging as well as any other reports.

The CPB procedure is carried out under general or spinal anaesthesia.

Patients who consent to the study and undergo the CPB procedure will follow the medication regimen described below

- At the time of consent
 - A prescription for a phosphate enema, 2 glycerine suppositories, an alpha-blocker and ciprofloxacin is given to the patient.
- 7 days prior to the procedure
 - Any anti-platelet agents (e.g. aspirin or clopidogrel) are stopped. Anticoagulants (e.g. warfarin or heparin) are stopped after consultation with local guidelines/haematologists.
 - An alpha-blocker (e.g. tamsulosin or alfuzosin) should be started, unless patient is on an alpha-blocker already. This will be continued for at least 2 weeks post-biopsy.

- Bowel preparation
 - A phosphate enema is administered prior to the procedure. This should ideally be administered at home, the evening prior to the procedure. If it cannot be administered at home, then a phosphate enema or glycerine suppository will be given on the morning of the procedure by nursing staff on admission at least 30-60 minutes prior to procedure.
 - If the phosphate enema cannot be taken by the patient the night before, he is advised to use one glycerine suppository the evening prior to the procedure. To help with emptying of bowels, to reduce faeces.
 - One glycerine suppository will be taken by the patient early in the morning on the day of procedure when they arrive in hospital, unless they have taken a phosphate enema in the morning.

Venous Thromboembolism Prophylaxis

Is performed as per the local guidelines of the site where the patient has their CPB. Compression stockings as a minimum.

Antibiotic regimen

- g) CIPROFLOXCIN 500MG twice daily with the first dose given the evening prior to the combined biopsy and then continued for 5 days.
- h) AMIKACIN 7mg/kg or GENTAMICIN 160mg (if local microbiology guidelines prevent use of amikacin) on induction.
- i) METRONIDAZOLE 1g suppository to be given immediately after TRUS guided biopsies.

Additional Medications

- c) Dexamethasone 0.15mg/kg to be given at induction by the anaesthetist.
- d) Lactulose 10ml tds/prn to be given after the biopsy.

Every patient is catheterised with a 16Ch or 14Ch catheter under sterile conditions.

Infection / Sepsis

Sepsis

Sepsis in this trial is defined as a proven infection causing systemic inflammatory response syndrome (SIRS)

- Body temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$
- Heart rate > 90 beats per minute
- Respiratory rate > 20 breaths per minute or $\text{PaCO}_2 < 32\text{mmHg}$ ($<4.3\text{ KPa}$) or need for mechanical ventilation
- White cell count $>12,000\text{ cells/mm}^3$ or $<4,000\text{ cells/mm}^3$ or $>10\%$ immature (band) forms

If an investigator is classifying an event as sepsis and it does not fit the criteria above, he/she must make this clear to the research team.

Who to notify

During office hours, the treating physician or nurse should contact the PROMIS team immediately (as found on the patient card) to notify them of the problem and seek further advice if relevant. If the patient card is not available, please see the [site contacts at the end of this document](#). If the patient is seen outside of office hours, the treating clinician must decide on the most appropriate treatment and the PROMIS team should be contacted as soon as possible, after this.

Medical Examination

Men who present with symptoms or signs of urinary infection and/or sepsis, should be fully evaluated. This evaluation should include history, examination, urine dipstick testing and a mid-stream urine sample to be sent to microbiology. If there are symptoms or signs of sepsis blood cultures should also be sent.

A full check should be made of the antibiotics that have been so far given. As a minimum, patients should have been given an antibiotic regimen as described in the section above.

Antibiotic therapy

Antibiotic therapy is to be started at the discretion of the treating physician or nurse. If the man is to be treated with antibiotics for a presumed urinary infection, it is likely that the prophylaxis has not worked, so a different antibiotic regimen should be prescribed. The antibiotic regimen prescribed should ALWAYS be discussed with the local microbiology department and this advice documented.

Expectations of PROMIS Research Team (and treating clinical team)

If the patient is admitted for intravenous antibiotics, the local PROMIS team should notify this as a Serious Adverse Event (SAE) and obtain daily updates on the patient's

progress. The SAE form must be submitted to the MRC CTU within 24 hours of the local team becoming aware of the event. Follow-up reports must be submitted as and when they become available and events must be tracked and updated until completely resolved.

If the patient is sent home with antibiotics, the local PROMIS research team will log the event for daily updates. The local PROMIS research team will call the patient the following day to determine health status and take any appropriate medical action. The patient should be asked to call the research team directly if symptoms deteriorate or if there are any concerns.

The local PROMIS research team will check the MSU (and blood cultures if sent) result every day or until the final result is issued (this is usually at day 2 or 3).

Positive cultures

- If the cultures are positive, the local PROMIS team should consult with the local microbiology team and ensure that the patient is on the correct antibiotic therapy. If the antibiotics are not correct, the correct antibiotics should be issued immediately to the patient and the patient's GP notified.

Negative cultures

- If the MSU is negative, and the patient's symptoms are not resolving, the patient should be seen urgently for medical review (history and full examination) and further cultures of urine (and blood if appropriate) sent. Consideration should be given to an evaluation of bladder emptying. Medical management will subsequently depend on specific findings. If urinary infection/sepsis is still suspected, urgent discussion with microbiology should occur and consideration given to inpatient admission for intravenous antibiotics.
- If the cultures are negative, and the patient's symptoms are resolving, the antibiotic course that has already been prescribed should be completed.

Key contacts

The PROMIS Team at the MRC CTU at UCL (promis@ctu.mrc.ac.uk) can be contacted during office hours for general information, but will not be able to offer any clinical advice.

Site (Role)	Contact Name	E-mail address
UCLH (Chief Investigator)	Professor Mark Emberton	Markemberton1@btinternet.com
UCLH (Principal Investigator)	Hashim Uddin Ahmed	Hashim.ahmed@ucl.ac.uk
UCLH (Research Fellow for PROMIS trial)	Shater Bosaily	A.Shater@uclh.nhs.uk
UCLH (Research Nurse)	Rebecca Scott	rebecca.scott@uclh.nhs.uk
Basingstoke (Principal Investigator)	Richard Hindley	Richard.Hindley@bnhft.nhs.uk
Basingstoke (Co-Investigator)	Timothy Nedas	Tim.Nedas@hhft.nhs.uk
Basingstoke (Clinical Trials Practitioner)	Abigail Edwards	Abigail.Edwards@bnhft.nhs.uk

14.3.4. Reporting results to patients



Developed with the NCRI Prostate Clinical Studies Group
Part of the NIHR National Cancer Research Network Portfolio
ISRCTN - 16082556
UCL reference - 11/0009
REC reference - 11/LO/0185



Evaluation of multi-parametric magnetic resonance imaging in the diagnosis and characterisation of Prostate Cancer

Reporting results to patients

Standard Operating Procedures

v04.00 07 MAY 2014

Authors		
Louise Brown Project Lead	Signature	Date:
Cybil Adusei Trial Manager	Signature	Date:
Reviewed and Authorised by		

Yolanda Collaco-Moraes Clinical Project Manager	Signature	Date:
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Revision History

Version	Author/s	Date	Reason for Revision
2.00	Sophie Stewart Cybil Kwakye	26 th – 31 st July 2012	<ul style="list-style-type: none"> - MRC CTU will be responsible for releasing results to sites. - Flow chart and external reports web link inserted.
3.00	Katie Thompson Cybil Adusei	15 th May – 16 th September 2013	<p>Changes for main phase of study.</p> <ul style="list-style-type: none"> - Site staff will be responsible for checking and downloading TPM and TRUS results. - MRC will only release MRI reports.
3.01	Cybil Adusei	<i>17th April 2014 – 7th May 2014</i>	<ul style="list-style-type: none"> - Figure 1 updated - MRI reports will no longer be e-mailed to sites. They will be stored on the secure FTP server that sites will have access to.

MRC will not release the MRI report until the trial results tracker indicates that both TPM and TRUS reports are available on the MRC CTU PROMIS online database. No reports are to be uploaded onto the hospital system (e.g. CDR or PACS) until the results tracker indicates that a complete set of results are available. The order for local or central MRI reports and TRUS or TPM results is interchangeable.

Obtaining PROMIS patient results

Figure 1 shows the order that radiology and pathology results become available for PROMIS patients. When all results have been reported, the local MRI report will be released onto the secure File Transfer Portal (FTP) server by MRC CTU staff and the TPM and TRUS will be available for download on the MRC reports system. All reports must be downloaded for the patient's End of Study visit.

A nominated member or members of the local research team will be in charge of collating available results from these procedures and arranging for them to be released to the Clinician holding the final study visit. It will be this person's responsibility throughout the PROMIS patient pathway to maintain blinding, i.e. keep all staff (including Clinicians, Histopathologists, Radiologists) and patients blinded from these results until the appropriate time.

The appropriate time for unblinding is when all three study procedures have been completed (MP-MRI, template and TRUS biopsies) AND all the results from these procedures are available. This nominated person must be identified as being in charge of this task on the site's delegation log, and an up to date copy of this must be sent to the Trial Manager at the MRC CTU.

Figure 1

Step-by-step procedure

- 1) MRI scan is read by local Radiologist and report is emailed as a pdf to the CTU
- 2) MRI scan is read by central Radiologist(s) and report is emailed as a pdf to the CTU
- 3) CTU stores the MRI reports on receipt of email
- 4) Pathologists enter pathology data from template and TRUS biopsies
- 5) The nominated staff member checks the MRC CTU online database for the availability of patient results as frequently as possible and required.
- 6) When both the TPM and TRUS results are available, the nominated staff member downloads the reports as pdf files.
- 7) The MRI report should be downloaded as a pdf from the MRC CTU FTP server.

- 8) The nominated site staff member can then release the results to the Clinician responsible for the patient to enable local standard care to continue in a timely fashion (discussion at Multidisciplinary meeting and patient).

Keeping track of the results status for a particular patient

The status of a patient's results can be viewed at any time using the 'Results Tracker'. It can be accessed using the following weblink:

<https://ctuapps.ctu.mrc.ac.uk/DSRTEExternal>

TPM and TRUS biopsy results can also be accessed by the research staff at the site using the link above. To protect the blinding, these results will only become available when both biopsy results have been signed off.

MRI reports can be accessed using the MRC CTU secure file transfer portal. Details on how to access this system can be found in the tracking patient results and downloading reports training slides.

Username and passwords are required to access the two systems mentioned above. Access details are issued by the MRC CTU, please contact MRCCTU.PROMIS@ucl.ac.uk for login details to access this system.

Only staff members delegated and signed off by the principal investigator to collate results from study procedures will be granted access to these systems.

In the event that any of the MRC CTU's online systems cannot be accessed, please e-mail MRCCTU.PROMIS@ucl.ac.uk.

N.B. The results reports are trial-related documents and we do not currently have ethical approval for printed versions of these to be given to patients. Results should be discussed in the consultation as they would in standard practice.

Planning the patient's End of Study visit (Visit 4)

The booking and timing of the patient's end of study visit needs to be planned. The nominated person who is collating the patient's results must therefore liaise with the staff booking patient appointments.

The end of study visit should be timed to be as soon as possible after the results are available. If the date of the combined biopsy procedure is known, potentially, this last study visit could be planned to occur no sooner than 15 working days after the date of the combined biopsy procedure. This should ensure that results are available, since the pathologists are asked to report results within 15 working days.

14.4. Case report forms

14.4.1. Patient registration form

14.4.2. MP-MRI

Patient's Initials: Date of Birth: Trial No.: Reporter: ☐ Local ☐ Central ☐ Additional ☐
Hospital Number: Scan Date:
PSA ng/ml: Tesla scanner: 1.5 ☐ OR 3.0 ☐ Are you blind to all results for this patient? Yes ☐ No ☐

1. SIZE OF PROSTATE

Transverse cm Anterior-Posterior cm Cranio-Caudal cm Volume cm³

If gland volume is $\geq 100\text{cm}^3$ submit this form immediately to the MRC CTU and complete a withdrawal form.

2. SECTOR (for UCL Definition Two disease) (Report strictly in order, and put a value 1-5[†] in each ROI). P = Posterior $< 1.7\text{cm}$ (measured from posterior capsule)

	T2	T2 + DW	T2 + DW + DCE
Base			
Mid			
Apex			

Risk category	Disease Threshold	MRI Score [†] (1-5)		
		R	L	Overall
Any cancer	Any Disease			
Definition Two (Primary outcome)	$\geq 0.2\text{cc}$ and/or $\geq 3+4$			
Definition One	$\geq 0.5\text{cc}$ and/or $\geq 4+3$			
Dominant Gleason 4	$\geq 4+3$			

3a. INDIVIDUAL LESIONS (Please draw and number measurable lesions on diagram below)

Base

Mid

Apex

Right Left

3b. INDIVIDUAL LESIONS

(Using the lesions drawn in 3a please score each lesion on the table below)

Lesion No.	T2	D	C	All	Curve 1=Slow rise 2=Flat 3=Early peak	ADC	Zone PZ/TZ/CZ/ Combination	Max diameter	Volume (cm ³) or 'Diffuse'	Distance from posterior capsule	Estimated Gleason Grade	Estimated Cancer Significance
	MRI Score [†] (For T2, D, C: 1-5 as on ESUR 2012 guidelines)				1-3	Value		mm		mm	e.g. 3+4	Not sign/Def 2/Def 1
1											+	
2											+	
3											+	
4											+	
5											+	
6											+	

4. STAGING

	Vesicles involved?	Extra-capsular?	Sphincter (T4)?	Rectum (T4)?	Nodes?
MRI Score [†] (1-5)					
If score > 2 , Left, Right or Bilateral?					

Submit this form immediately and complete a withdrawal form if giving a score of 4 or 5

If score for nodes > 2 , max short axis nodal diameter? (mm)

† MRI Score
1=Highly likely benign
2=Likely benign
3=Equivocal
4=Likely malignant
5=Highly likely malignant

Signature: Author Name: Report Date:

Please email a scanned copy to MRCCTU.PROMIS@ucl.ac.uk

14.4.3. Biopsy checklist

Patient's Initials: Date of Birth: Trial Number:

Hospital Number:

1. ASA Grade

- ☐ 1 = Normal, healthy
☐ 2 = Mild, systemic disease
☐ 3 = Severe, systemic disease
☐ 4 = Severe, systemic disease, constant threat to life

2. Was the EQ-5D questionnaire given to the patient?

- ☐ 0 = No
☐ 1 = Yes

3. Charlson Co-morbidity Score (Does the patient have any of the following?)

	No	Yes
Myocardial Infarction	<input type="checkbox"/>	<input type="checkbox"/>
Congestive Cardiac Failure	<input type="checkbox"/>	<input type="checkbox"/>
Peripheral Vascular Disease	<input type="checkbox"/>	<input type="checkbox"/>
Chronic Pulmonary Disease	<input type="checkbox"/>	<input type="checkbox"/>
Cerebrovascular Disease	<input type="checkbox"/>	<input type="checkbox"/>
Dementia	<input type="checkbox"/>	<input type="checkbox"/>
Ulcers	<input type="checkbox"/>	<input type="checkbox"/>
Connective Tissue Disease	<input type="checkbox"/>	<input type="checkbox"/>
Hemiplegia	<input type="checkbox"/>	<input type="checkbox"/>
Leukaemia	<input type="checkbox"/>	<input type="checkbox"/>
Malignant Lymphoma	<input type="checkbox"/>	<input type="checkbox"/>
AIDS	<input type="checkbox"/>	<input type="checkbox"/>

4. Charlson Co-morbidity Score (Does the patient have any of the following conditions? Please tick only one answer per condition)

	None	Without end organ damage	With end organ damage
Diabetes Mellitus	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

	None	Non-Metastatic	Metastatic
Malignant Solid Tumour	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

	None	Mild	Moderate	Severe
Liver Disease	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Renal Disease	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

5. Date of combined prostate biopsy procedure

6. Was Template Prostate Mapping (TPM) biopsy performed according to protocol?

- ☐ 0 = No (please complete question 6a and a withdrawal form)
☐ 1 = Yes

6a. Why was Template Prostate Mapping (TPM) biopsy not performed according to protocol?

- ☐ 0 = Limited TPM performed
☐ 1 = Other (please provide reason) Reason:

7. Name of physician performing the TPM biopsy procedure

8. Was TRUS biopsy performed according to protocol?

- ☐ 0 = No (please provide reason and complete withdrawal form, only if TPM was also not performed according to protocol)
☐ 1 = Yes Reason:

9. Did the same physician perform the TRUS biopsy procedure?

- ☐ 0 = No (if no, please name below)
☐ 1 = Yes

10. DECLARATION

I declare that the person reporting the MRI for this patient was not present in theatre at the time of the combined prostate biopsy procedure

Reporting physicians signature

11. According to the PROMIS protocol, TPM biopsies are to be performed before TRUS biopsies.

Please confirm that the procedure has been carried out according to protocol

- ☐ 0 = No (please contact PROMIS Trial Manager immediately if this has occurred)
☐ 1 = Yes

Signature: <input type="text"/>	Printed Name: <input type="text"/>	Date Completed: <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
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14.4.4. TPM

14.4.4.1. Main phase



TPM Biopsy Reporting Grid - Form 3b
V2.0 06th September 2013

Page 1 of 1

Patient's Initials: <input type="text"/>	Date of Birth: <input type="text"/>	Trial Number: <input type="text"/>
Hospital Number: <input type="text"/>	Date of TPM Biopsy: <input type="text"/>	

DECLARATION

I declare that I have no knowledge of the TRUS guided biopsy for this patient and I have not spoken to the other reporting Histopathologist specifically in relation to this patient's biopsies.

Reporting TPM Histopathologist Signature

(must be different from Histopathologist reporting TRUS results)

1. Was a second Histopathologist consulted?

☐ 0 = No
☐ 1 = Yes

2. If Yes, please provide Histopathologist's Name

3. Did this patient have a limited TPM?

☐ 0 = No
☐ 1 = Yes

4. TPM biopsy pathology ID number?

5. Individual zone details

Zone	a. Samples taken?	b. Presence of cancer?	c. Presence of other pathology? Inflammation, HGPIN or ASAP	d. Total number of cores	e. Max. core length
	No/Yes	No/Yes	No/Yes		mm
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					
20					

Signature: <input type="text"/>	Histopathologist Name: <input type="text"/>	Report Date: <input type="text"/>
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Date form received at CTU: <input type="text"/>	Date form entered onto database: <input type="text"/>	Initials of data enterer: <input type="text"/>
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Patient's Initials: Hospital Number: Date of Birth: Trial Number:

1. Did this patient have a limited TPM? ☐ 0 = No
1 = Yes
2. Individual zone information (1 – 10)

2. Individual zone information (1 – 10)													
	Zones Containing Cancer								Zones Not Containing Cancer				
					Gleason grade								
Zone	a. How many cores contain cancer?	Total cancer core length		Max cancer core length		f. 1°	g. 2°	h. 3°	i. Peri-neural invasion	j. Lymphovascular invasion	k. Severe inflammation	l. HGPIN	m. ASAP
	If 0, go to k - m If 1 or more go to b - j	b. UK	c. ISUP	d. UK	e. ISUP								
		mm	mm	mm	mm				No/Yes	No/Yes	No/Yes	No/Yes	No/Yes
1													
2													
3													
4													
5													
6													
7													
8													
9													
10													

Signature: Histopathologist Name: Report Date:

Please return a copy via fax to: 0207 670 4818

For office use only:
Date form received at CTU: Date form entered onto database: Initials of data enterer:

Patient's Initials: Hospital Number: Date of Birth: Trial Number:

3. Individual zone information (11 – 20)

	Zones Containing Cancer									Zones Not Containing Cancer			
						Gleason grade							
Zone	a. How many cores contain cancer?	Total cancer core length		Max cancer core length		f. 1°	g. 2°	h. 3°	i. Peri-neural invasion	j. Lymphovascular invasion	k. Severe inflammation	l. HGPIN	m. ASAP
	If 0, go to k - m If 1 or more go to b - j	b. UK	c. ISUP	d. UK	e. ISUP								
		mm	mm	mm	mm				No/Yes	No/Yes	No/Yes	No/Yes	No/Yes
11													
12													
13													
14													
15													
16													
17													
18													
19													
20													

Signature: Histopathologist Name: Report Date:

Please return a copy via fax to: 0207 670 4818

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TPM Biopsy Details Report - Form 3c Overall Summary
V2.0 06th September 2013

Patient's Initials: <input type="text"/>	Date of Birth: <input type="text"/>	Trial Number: <input type="text"/>
Hospital Number: <input type="text"/>	Date of TPM Biopsy: <input type="text"/>	

1. TPM biopsy pathology ID number?

2. Overall Summary - Cancer

Cancer					
Cancer core length (mm)		Overall Gleason sum score	Maximal Gleason sum score	Peri-neural invasion	Lympho-vascular invasion
UK	ISUP	Primary + Secondary	Primary + Secondary	No/Yes	No/Yes

3. Overall Summary - No Cancer

No Cancer		
Presence of severe inflammation	Presence of HGPIN	ASAP
No/Yes	No/Yes	No/Yes

Signature: <input type="text"/>	Histopathologist Name: <input type="text"/>	Report Date: <input type="text"/>
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Please return a copy via fax to: 0207 670 4818

For office use only:

Date form received at CTU: <input type="text"/>	Date form entered onto database: <input type="text"/>	Initials of data enterer: <input type="text"/>
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14.4.4.2. Pilot phase

**PROMIS****TPM Biopsy Reporting Grid - Form 3b**

V1.0 24 February 2012



Page 1 of 1

Patient's Initials:	<input type="text"/>	Date of Birth:	<input type="text"/>	Trial Number:	<input type="text"/>
Hospital Number:	<input type="text"/>	Date of TPM Biopsy:	<input type="text"/>		

DECLARATION

I declare that I have no knowledge of the TRUS guided biopsy for this patient and I have not spoken to the other reporting Histopathologist specifically in relation to this patient's biopsies.

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
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Reporting TPM Histopathologist Signature

(must be different from Histopathologist reporting TRUS results)

1. Was a second Histopathologist consulted?

<input type="checkbox"/>	0 = No
<input type="checkbox"/>	1 = Yes

2. If Yes, please provide Histopathologist's Name**3. TPM biopsy pathology ID number?**

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
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4. Area assessed

Apex	<input type="checkbox"/>	Base	<input type="checkbox"/>
------	--------------------------	------	--------------------------

5. Length of cores in mm

- ☐ If no sample is taken at coordinates, please leave square empty
☐ If a sample contains cancer or other pathology, please circle the core length value to indicate this
☐ Mark **x** where a sample has been taken, but is not assessable

	A	a	B	b	C	c	D	d	E	e	F	f	G
7													
6.5													
6													
5.5													
5													
4.5													
4													
3.5													
3													
2.5													
2													
1.5													
1													

6. Do any of the core samples show signs of cancer, severe inflammation, HGPIN or ASAP?

<input type="checkbox"/>	0 = No
<input type="checkbox"/>	1 = Yes (If yes, please complete form 3c)

Signature:

Histopathologist Name:

Report Date:

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
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Please return a copy via fax to: 0207 670 4653

For office use only:

Date form received at CTU: dd - mm - yyyy

Date form entered onto database: dd - mm - yyyy

Initials of data enterer:

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
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14.4.5. TRUS

14.4.5.1. Main phase



TRUS Guided Biopsy Reporting - Form 3d
V2.0 06th September 2013

Page 1 of 1

Patient's Initials: Date of Birth: Trial Number:

Hospital Number: Date of TRUS Guided Biopsy:

DECLARATION

I declare that I have no knowledge of the TPM for this patient and I have not spoken to the other reporting Histopathologist specifically in relation to this patient's biopsies.

Reporting TRUS Histopathologist signature

(Must be different from Histopathologist reporting TPM results)

1. Was another Histopathologist consulted?

☐ 0 = No
☐ 1 = Yes

2. If yes, please provide Histopathologist's name

3. TRUS guided biopsy pathology ID number?

4. INDIVIDUAL CORES

	a. Length of core	b. Presence of cancer	Cancer						No Cancer		
			c. Cancer core length		Gleason grade			g. Peri-neural invasion	h. Lympho-vascular invasion	i. Presence of severe inflammation	j. Presence of HGPIN (Please strike through i-k if NO, cancer present)
			UK	ISUP	d. 1°	e. 2°	f. 3°				
	mm	(No - Go to i - k Yes - Go to c)	mm	mm				No/Yes	No/Yes	No/Yes	No/Yes
A: R lat base											
B: R lat mid											
C: R lat apex											
D: R parasag base											
E: R parasag mid											
F: R parasag apex											
G: L lat base											
H: L lat mid											
I: L lat apex											
J: L parasag base											
K: L parasag mid											
L: L parasag apex											

5. Overall Summary

(If cancer has been reported, please complete the left hand table. If no cancer has been reported, please complete the right hand table.)

Cancer						No Cancer		
Cancer core length (mm)		Overall Gleason sum score	Maximal Gleason sum score	Peri-neural invasion	Lympho-vascular invasion	Presence of severe inflammation	Presence of HGPIN	ASAP
UK	ISUP	Primary + Secondary	Primary + Secondary	No/Yes	No/Yes	No/Yes	No/Yes	No/Yes
		+	+					

Signature: Histopathologist Name: Report Date:

Please return a copy via fax to: 0207 670 4818

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14.4.5.2. Pilot phase

14.4.6. End of study



SIDE EFFECTS

Side effects	No	Yes
MP-MRI		
Pain/discomfort		
Allergic reaction to contrast medium		
Other, please specify _____		
Other, please specify _____		
Combined Prostate Biopsy Procedure		
Pain/discomfort		
Dysuria		
Haematuria		
Haematospermia		
Erectile Dysfunction (requiring medication, injection therapy or devices)		
Urinary Tract infection(s) <i>(only answer 'yes' if infection has been confirmed by lab test)</i>		
Systemic urosepsis (If yes, please complete SAE Form)		
Acute urinary retention		
Symptoms associated with general/spinal anaesthetic		
Other, please specify _____		
Other, please specify _____		
Other, please specify _____		

If any of the above meet SAE criteria, please complete an SAE Form.

2. Please confirm that the results of the procedures have been discussed with the patient today

0 = No
1 = Yes

PATIENT MANAGEMENT

3a. Have future management options been discussed?

☐ 0 = No
☐ 1 = Yes
☐ 2 = Not applicable
☐ 3 = No, a further appointment is required

3b. If yes, what is the likely management? (Please tick all appropriate boxes)

☐ No management ☐ Active surveillance ☐ Radical Prostatectomy ☐ Radiotherapy
☐ Chemotherapy ☐ Other _____

Signature:

For office use only:

Date form received
at GTU: dd - mm - yyyy

Date form entered
onto database : dd - mm - yyyy

Initials of data enterer:				
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End of Study - Form 4
V2.0 06th September 2013

Page 2 of 2

Patient's Initials: Date of Birth: Trial Number:

4. Has the patient taken any medications whilst taking part in PROMIS?

☐ 0 = No 1= Yes (If yes, and details not already provided on an SAE report form, please provide details in the table below.)

Treatment Give generic name	Total daily dose	Route 1=Oral 2 =Intravenous 3=Subcutaneous 4=Other	Start Date dd/mm/yyyy	Ongoing 0=No 1=Yes	End Date dd/mm/yyyy

Continue on a separate sheet if necessary

5. USE OF COMMUNITY AND HOSPITAL HEALTH SERVICES SINCE TAKING PART IN PROMIS

Note - These questions relate to prostate cancer or tests for potential prostate cancer

- a. How many times did the patient visit their GP?
- b. How many times was the patient visited by their GP?
- c. How many times did the patient visit a practice nurse/district nurse?
- d. How many times did the patient visit the hospital, as an out patient?
- e. How many in-patient nights did the patient spend in hospital?
- f. How many hours did the patient spend in ITU?
- g. How many additional non-protocol, condition related procedures has the patient had?

Please list below if any

- h. Did the patient have a trial without catheter? ☐ 0 = No
☐ 1 = Yes

6. Would the patient like to receive a summary of the study results when the study is complete?
Please note this may be in 5-6 years time

☐ 0 = No
☐ 1 = Yes

Please remember to ask the patient to complete their last EQ-5D and thank them for participating in this study.

Signature: <input type="text"/>	Printed Name: <input type="text"/>	Date Completed: <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>
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14.4.7. Serious adverse events



Serious Adverse Event Reporting – Form 5
V2.0 06th September 2013

Page 1 of 2

Patient's Initials: Date of Birth: Trial Number:

Hospital Number: Responsible Clinician:

Hospital:

1. Type of report

☐ 1 = First
☐ 2 = Follow Up If follow up specify number

2. Why was the event serious?

- ☐ 1 = Resulted in death
☐ 2 = Life-threatening
3 = Required inpatient hospitalisation or Prolongation of existing hospitalisation
4 = Persistent or significant disability/incapacity
5 = Congenital anomaly/birth defect
6 = Other important medical conditions

3. Where did SAE take place?

- ☐ 1 = Hospital
☐ 2 = Home
☐ 3 = Other
If Other, please specify:

Details of SAE

4. Main diagnosis/symptom (Enter the MAIN EVENT in the first row, followed by any associated symptoms)	5. Date of onset dd/mm/yyyy	6. SAE Status 1 = Resolved 2 = Resolved with sequelae 3 = Ongoing 4 = Worsened 5 = Fatal	7. Date resolved dd/mm/yyyy
Associated symptoms:			

8. Most recent trial visit number (please tick)
(Please refer to PROMIS Trial Schema for more information)

☐ 1 ☐ 2 ☐ 3 ☐ 4

9. Trial Procedure	10. Date of Procedure dd/mm/yyyy	11. Causal relationship to SAE 1 = Definitely 2 = Probably 3 = Possibly 4 = Unlikely 5 = Not related 6 = Administration 7 = Unassessable	12. Expectedness* 1 = Expected 2 = Unexpected	13. Action taken due to SAE 0 = None 1 = Prescription 2 = Hospitalisation required 3 = Hospitalisation prolonged 4 = Withdrawal from Study 5 = Other (if Other, please provide details below)

* Was the event one of the recognised undesirable effects of the trial procedure? (Please see Section 7. Safety Reporting of the PROMIS Protocol)

Other treatments (Exclude any therapy given for management of SAE; include concomitant medication, radiotherapy and palliative care. Continue on a separate sheet if necessary)

14. Treatment Give generic name	15. Total Daily Dose	16. Route 1 = Oral 2 = Intravenous 3 = Subcutaneous 4 = Other	17. Start Date dd/mm/yyyy	18. Ongoing 0 = No 1 = Yes	19. End Date dd/mm/yyyy	20. Causal relationship to SAE 1 = Definitely 2 = Probably 3 = Possibly 4 = Unlikely 5 = Not related 6 = Administration	21. Action taken due to SAE 0 = None 1 = Dose reduction 2 = Treatment delayed 3 = Treatment reduction & delayed 4 = Treatment stopped

Signature:

Printed Name:

Date Completed:

Please fax to 0207 670 4818 within 1 working day of identification of event FAO: PROMIS Trial Manager

For office use only:

Date form entered onto database : - -

Initials of data enterer:

Patient's Initials: <input type="text"/>	Date of Birth: <input type="text"/>	Trial Number: <input type="text"/>
Hospital Number: <input type="text"/>	Responsible Clinician: <input type="text"/>	
Hospital: <input type="text"/>		

22. Describe serious adverse event (Include manifestation & progression of event, any treatments given in response to the event and any relevant tests carried out e.g. WBC, neutrophil count. Continue on a separate sheet if necessary).

Diagnostic Tests:

23. Test name	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
24. Date	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
25. Normal range	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
26. Result (+ units)	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>

27. What is your assessment of the implications, if any, for the safety of study participants and how will these be addressed?

28. Date you became aware of this event

29. Do you consider this event likely to have been caused by anything other than the procedure/s listed previously on this form? ☐ 0 = No
☐ 1 = Yes If Yes specify (include medical history, drug or alcohol abuse, family history, findings from special investigation)

Signature: <input type="text"/>	Printed Name: <input type="text"/>
Contact Telephone: <input type="text"/>	Date Completed: <input type="text"/>

CTU Clinical Reviewer Use ONLY			Date checked by Clinical Reviewer <input type="text"/>	
Reportable Event <input type="checkbox"/>	Other SAR <input type="checkbox"/>	Unrelated SAE <input type="checkbox"/>		
Not an SAE <input type="checkbox"/>	Sepsis <input type="checkbox"/>			
Comments: <input type="text"/>			MRC CTU Staff Use ONLY	
<input type="text"/>			Event No <input type="text"/>	
<input type="text"/>			If reportable event, date sent to MREC <input type="text"/>	
<input type="text"/>			Form checked and Ready to file <input type="text"/>	
Body system: <input type="text"/>			MRC CTU Staff Signature <input type="text"/>	
Clinical Reviewer <input type="text"/>				

For office use only:

Date form entered onto database :

Initials of data enterer:

14.4.8. Withdrawal



Withdrawal – Form 6
V2.0 06th September 2013

Page 1 of 1

Patient's Initials: Date of Birth: Trial Number:

Hospital Number:

1. Date patient withdrew from PROMIS

2. Reason patient withdrew from PROMIS

- ☐ 1 = Patient choice
☐ 2 = Scan was unreadable and unrepeatable
☐ 3 = CPB procedure could not be performed according to trial protocol
☐ 4 = MP-MRI reveals a gland of ≥ 100 cc
☐ 5 = MP-MRI reveals apparent T4 prostate cancer or involved lymph nodes or colorectal/bladder invasion
☐ 6 = Other, please specify _____

3. Type of withdrawal

- ☐ 1 = Complete withdrawal from further study procedures and any future follow up
☐ 2 = Partial withdrawal from study procedures but allowing the possibility of further follow up

4. At what time point did patient withdraw?

- ☐ 1 = **Before** MP-MRI
☐ 2 = **After** MP-MRI and **before** combined prostate biopsy procedure
☐ 3 = **After** MP-MRI and TPM biopsy procedure (before TRUS biopsy)
☐ 4 = **After** MP-MRI and combined prostate biopsy procedure (after TPM and TRUS)

5. Comments

Include more information on withdrawal if possible

Signature: Printed Name: Date Completed:

Please return a copy via fax to: 0207 670 4818

For office use only:

Date form received at CTU: Date form entered onto database: Initials of data enterer: