THE ROLE OF MRI-TARGETED BIOPSY IN THE DIAGNOSIS OF PROSTATE CANCER

Thesis submitted to University College London

for the degree of Doctor of Philosophy

Veerappan Kasivisvanathan

Supervisors:

Professor Caroline M Moore

Professor Mark Emberton

Professor Jan van der Meulen

I, Veerappan Kasivisvanathan, 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.

Current word count: 61,402

Abstract

Introduction

The existing standard of care for the diagnosis of prostate cancer, transrectal ultrasound guided prostate (TRUS) biopsy, can miss clinically important prostate cancer and over detect clinically unimportant cancer.

Methods

I evaluated MRI followed by a targeted biopsy to MRI-suspicious areas (MRI-TB) as an alternative diagnostic test to TRUS biopsy in men with clinical suspicion of prostate cancer based on raised prostate specific antigen or abnormal digital rectal examination. I first evaluated MRI-TB in a single institution study compared to a detailed test of transperineal prostate biopsy to establish the technique's promise. An international consortium with expertise in MRI-TB was established, amongst which we created reporting guidelines for studies of MRI-TB. In this consortium, we designed and carried out an international multicentre randomized-controlled trial comparing MRI-TB to TRUS biopsy in the detection of cancer.

Results

In a single institutional study, I showed that MRI-TB detected a similar amount of clinically significant cancer to a transperineal prostate biopsy whilst requiring fewer biopsies. Within the START (STAndards for Reporting studies of MRI-Targeted biopsy) consortium, we developed international MRI-TB reporting guidelines and PRECISION (PRostate Evaluation for Clinically Important disease: Sampling using Image-guidance Or Not?), a 500 patient, 23-centre, randomized-controlled trial, comparing MRI-TB and TRUS biopsy. PRECISION showed that MRI-TB detected 38% of men with clinically significant prostate cancer (≥Gleason 3+4) compared to 26% for TRUS biopsy (p=0.005), detected fewer men with clinically unimportant prostate cancer (Gleason 3+3) (9 vs 22%, respectively, p < 0.001) and required fewer biopsies (median of 4 vs 12, respectively). Further,

28% of men in the MRI arm could avoid a biopsy and its discomfort and risks altogether.

Conclusions

MRI±TB is an attractive test to rival TRUS biopsy as the standard of care for the diagnosis of prostate cancer. It can more efficiently identify men who would benefit from treatment and avoids the diagnosis of men who are less likely to benefit.

Impact statement

This thesis evaluates MRI-targeted prostate biopsy, a diagnostic technique for prostate cancer, in men with clinical suspicion of the disease. It brings new knowledge on how to report studies of MRI-TB and on the efficacy of the technique compared to the current standard of care, transrectal ultrasound guided prostate biopsy. It also brings new knowledge on whether the skills required to use the technology can be learned.

This work shows that MRI-TB is a valid alternative diagnostic test to the existing standard of care, with a notable number of advantages. Fewer men need to undergo biopsy and those that do require far fewer biopsy cores. MRI-TB was shown to detect more men with clinically important cancer that is likely to benefit from treatment and fewer men with clinically unimportant cancer that is unlikely to benefit from treatment.

The findings of this thesis are directly applicable to clinical practice. All of the clinical efficacy studies carried out in this body of work were carried out within clinical settings. The main randomized controlled trial evaluating the efficacy of MRI-TB compared to TRUS biopsy was a pragmatic international multi-centre randomized-controlled trial, thus the findings of this thesis are generalizable to other healthcare centres around the world who manage men with suspected prostate cancer. Given one million men typically undergo biopsy in Europe and the U.S. every year, this work will lead to massive benefit for men with suspected prostate cancer around the world and will influence the practice of hundreds of medical centres around the world. This work has the potential to improve the quality of life of these patients and their families, their treatment options and ultimately their survival.

This work has led to closer multidisciplinary ties with the medical specialities of urology, radiology, pathology and the field of engineering. This will promote collaboration between these departments that will help in the development of novel future innovations that can benefit patient care. This work has led to developments in the methods of teaching of clinicians to use the technology and

will influence the curriculum adopted by international uroradiological organisations for training of their workforce.

The work has also allowed further research on optimising the diagnostic pathway of prostate cancer to be carried out and will promote further research into optimising the technique of MRI-TB to lead to the greatest patient benefit. This work will also influence national and international healthcare bodies in their recommendations for the diagnosis of prostate cancer and will therefore likely influence government policy in allocation of resources for prostate cancer.

Acknowledgements

From when I first made a decision to dedicate myself to undertaking a PhD, it has been a fascinating and rewarding journey in which I have learnt and achieved things that I never thought would be possible. An intellectual curiosity, desire to improve patient care and commitment to finishing a pathway that I have embarked on are what have driven me to completing this task. I am very grateful to my supervisors Caroline Moore, Mark Emberton and Jan van der Meulen, who have each shared their valuable wisdom with me and have enabled me to grow into an academic clinician. I thank them for the time they devoted to me and in trusting the decisions that I made.

This journey is one that involved sacrifice and I am eternally grateful to my family, particularly my wife Lukshmy, son Ashwin, mother, father and brother, for sharing me with Science. They provided me with invaluable support, motivation and flexibility throughout the process and it would not have been possible without them.

Table of Contents

Chapter 1 Introduction 19
1.1 Prostate cancer epidemiology 19
1.2 Risk factors for prostate cancer 19
1.3 Histopathological features of prostate cancer 21
1.4 History of prostate cancer diagnosis 22
1.5 Clinical significance of prostate cancer 23
1.6 Errors associated with TRUS biopsy 23
1.7 Transperineal prostate biopsy 24
1.8 Challenges in prostate cancer research 25
1.9 Adjuncts and alternatives to PSA in the diagnostic pathway 28
1.10 Emerging role of prostate MRI 29
1.11 MRI-targeted biopsy 36
1.12 Existing knowledge on MRI-targeted biopsy 37

Chapter 2 MRI-targeted biopsy compared to systematic biopsy in a single institution setting 40
2.1 Introduction 40
2.2 Methods 41
2.3 Results 46
2.4 Discussion 53

2.5 Statement of contribution 57

2.6 Related publication 58

Chapter 3 Establishing standards for reporting of studies of MRI-targeted biopsy 59

3.1 Introduction 59

3.2 Methods 60

3.3 Results 66

3.4 Discussion 88

3.5 Statement of contribution 93

3.6 Related Publication 94

Chapter 4 Designing a study to change the standard of care from TRUS biopsy to MRI-Targeted biopsy 95

4.1 Introduction 95

4.2 Study design considerations 96

4.3 Randomized trial design comparing MRI-targeted to TRUS biopsy 99

4.4 Full study title 101

4.5 Study objectives 101

4.6 Trial Design 101

4.7 Setting 102

4.8 Inclusion criteria 102

4.9 Exclusion criteria 103

4.10 Interventions 105

4.11 Treatment Decision 107

4.12 Primary outcome 107

4.13 Secondary outcomes 107

4.14 Completion of the study 108

4.15 Patient withdrawal 109

4.16 Hypothesis 109

4.17 Sample size considerations 109

4.18 Timeline for recruitment 110

4.19 Randomization processes 110

4.20 Blinding 110

4.21 Data management 111

4.22 Data collection 111

4.23 Statistical analysis 115

4.24 Ethical considerations 121

4.25 Dissemination 125

4.26 Funding 125

4.27 Evaluating the pragmatism of the PRECISION study 126

4.28 Statement of contribution 129

4.29 Related Publication 131

Chapter 5 The PRECISION Trial results 143

5.1 Introduction 143

5.2 Results 143

5.3 Discussion 178

5.4 Statement of Contribution 186

5.5 Related Publication 187

Chapter 6 Assessing the ability of Urologists to learn how to interpret Prostate MRI information 188

6.1 Introduction 188

6.2 Methods 191

6.3 Results 197

6.4 Discussion 206

6.5 Statement of contribution 209

6.6 Related Publication 210

Chapter 7 Final discussion and future directions 211

7.1 Emerging data from recently published studies 211

7.2 Limitations of MRI-TB and future directions 214

7.3 Discussion and conclusion 219

Chapter 8 Appendices 222

References 230

Table of Tables

Table 1. 1: Correlation of proposed ISUP Gleason grade group with the modified Gleason grading system 22

Table 1. 2 A summary of the key features of the randomized trials evaluating PSA screening to reduce prostate cancer-specific mortality 26

Table 1. 3: Likert scale for suspicion of prostate cancer 33

Table 1. 4: Diagnostic performance of MRI versus TRUS biopsy in the detection of clinically significant cancer 34

Table 2. 1: MRI protocol 43

Table 2. 2: Summary of key patient characteristics 48

Table 2. 3: Table of agreement summarising cancer detection by MRI-targeted biopsy and transperineal template prostate biopsy 50

Table 2. 4: Cancer detection classified by prior biopsy status 51

Table 2. 5: Cancer detection using UCL definition 1 52

Table 2. 6: Cancer detection using Harnden definition 53

Table 3. 1: Institutions and researchers comprising the START consortium 61

Table 3. 2: Agreed terminology for MRI-targeted biopsy 66

Table 3. 3: Full list of items for scoring in round 2 and the level of agreement and consensus for each item 68

Table 3. 4: Table of agreement for histopathological results of MRI-targeted and systematic biopsies 83

Table 3. 5: Notable items scored with uncertainty 84

Table 3. 6: START Checklist of recommended items to report for MRI-targeted biopsies 85

Table 3. 7: Case report form consistent with reporting by START guidelines 87

Table 4. 1: A typical 2 x 2 table used to calculate diagnostic test performance . 97

Table 4. 2: Secondary outcomes of the PRECISION study 108

Table 4. 3: Table of anticipated recruitment 110

Table 4. 4: Participant timeline for data collection in the study 112

Table 4. 5: Treatment of patients within the intention to treat population 115

Table 4. 6: Treatment of patients within the intention to treat analysis in men who had more than one test 116

Table 4. 7: How to classify patients for modified intention to treat and per protocol analyses for the TRUS biopsy arm 117

Table 4. 8: How to classify patients for modified intention to treat and per protocol analyses for the MRI arm 118

Table 5. 1: Geographical distribution of recruitment of patients 144

Table 5. 2: Sites involved in the PRECISION Trial and their recruitment 145

Table 5. 3: Clinician experience in the PRECISION Trial as recorded at the start of the study 146

Table 5. 4: MRI protocols for sites taking part in PRECISION 148

Table 5. 5: Baseline Characteristics of population 152

Table 5. 6: Key MRI features in men in the MRI arm 154

Table 5. 7: Approaches and techniques used for MRI-targeted biopsy 155

Table 5. 8: Biopsy details of men undergoing MRI-targeted biopsy and TRUS biopsy 156

Table 5. 9: Detailed cancer detection comparison between MRI ± targeted biopsy and TRUS biopsy 158

Table 5. 10: Health-related quality of life at baseline, 24 hours after intervention and 30 days after intervention 161

Table 5. 11: Patient-reported complications 162

Table 5. 12: A table summarizing investigator-reported adverse events 163

Table 5. 13: Treatment decisions made for men in the study 165

Table 5. 14: A table summarizing outcomes of men undergoing further diagnostic tests after the protocol test 166

Table 5. 15: Agreement in concordant biopsy decision by PIRADSv2 score between local site radiologist and central quality control interpretation 168

Table 5. 16: Table of agreement between local site and central pathologist report for Gleason grading of cancer identified 169

Table 5. 17: Cost-effectiveness resource use sources and unit costs considered 170

Table 5. 18: Within trial resource use and total costs..... 176

Table 5. 19: Short-term cost-effectiveness outcomes from a UK health perspective..... 177

Table 6. 1: MRI protocols for the scanners used in the study 194

Table 6. 2: Participant experience and individual area under the curves for detection of significant cancer for Test 1 and Test 2..... 199

Table 6. 3: Summary characteristics of the patients used in the test cases..... 200

Table 6. 4: Average area under the curve for detection of clinically significant cancer in sub-groups at baseline (test 1) and post-teaching (test 2) 203

Table of Figures

Figure 1. 1: Global age-standardized incidence and mortality rates in 2018 for the top 10 most incident cancers 20

Figure 1. 2: UK incidence rate for prostate cancer from 1995-2012, age-standardised to a global population 21

Figure 1. 3: Transperineal sector biopsy schema 25

Figure 1. 4: A multiparametric MRI demonstrating an area suspicious for significant cancer 32

Figure 1. 5: PROMIS study schema 34

Figure 1. 6: Possible roles for a new diagnostic test 36

Figure 2. 1: 20-sector modified Barzell transperineal template biopsy schema . 45

Figure 2. 2: Summary of study flow 47

Figure 4. 1: Paired cohort design study comparing MRI-targeted biopsy to TRUS biopsy 98

Figure 4. 2: Randomized study design comparing MRI-targeted to TRUS biopsy 99

Figure 4. 3: PRECISION Trial Schema 102

Figure 4. 4: Example of TRUS biopsy technique 105

Figure 4. 5: Model consent form for PRECISION Study 122

Figure 4. 6: PRECIS-2 diagram showing degree of pragmatism of the PRECISION Trial design 128

Figure 5. 1: Recruitment rate in the PRECISION study 143

Figure 5. 2: Patient flow in the PRECISION trial 153

Figure 5. 3: Graphical depiction of the analyses of the primary outcome 157

Figure 5. 4: Graphical depiction of the cancer status of men given by PIRADSv2 score..... 160

Figure 6. 1: The structure of the 2-day training course. 191

Figure 6. 2: Average area under the curve for detection of clinically significant cancer at baseline (test 1) and post-teaching (test 2) at the whole gland level 201

Figure 6. 3: Average area under the curve for detection of clinically significant cancer at baseline (test 1) and post-teaching (test 2) at quadrant level 202

Figure 6. 4: Average area under the curve (AUC) for detection of clinically significant cancer at baseline (test 1) and post-teaching (test 2) for participants of different experience level of prostate MRI prior to the course. 204

Chapter 1 Introduction

1.1 Prostate cancer epidemiology

Prostate cancer has the second highest worldwide age-standardized incidence of any cancer with 29.3 occurrences per 100,000 people in 2018 (Figure 1. 1) [1]. It is the sixth highest leading cause of death from cancer with an age standardised mortality rate of 7.6 deaths per 100,000 people in 2018 (Figure 1. 1). From 1995 to 2012, prostate cancer incidence in the UK has increased by 1.7 times (Figure 1. 2). Compared to other cancers, prostate cancer has relatively good prognosis, with a 10-year survival of 84% for men in England and Wales in 2011 [2]. Survival though, does varies by whether the disease is localised to the prostate or not, with localised disease having a 1-year age standardised net survival of 100% but with disease invading surrounding organs having an 85% 1-year survival [2].

1.2 Risk factors for prostate cancer

Black men have a higher incidence of prostate cancer and in addition, this prostate cancer tends to be more aggressive [3]. There is also evidence that a strong family history of prostate cancer is associated with the development of prostate cancer. Approximately 5-10% of men have hereditary disease and specific mutations that have been identified include BRCA1, BRCA2 and HOXB12[4-6]. Environmental factors are also thought to play a role as noted by the higher incidence of cancer in Asian men moving to Western countries than Asian men remaining in their home countries [7].

Figure 1. 1: Global age-standardized incidence and mortality rates in 2018 for the top 10 most incident cancers

Reproduced from the International Agency for Research on Cancer [1]. Blue bars indicate incidence rate, red bars indicate mortality rate. Rates given in age standardized ratio (ASR) for the world per 100,000 (x-axis). Cancer type given on y-axis.

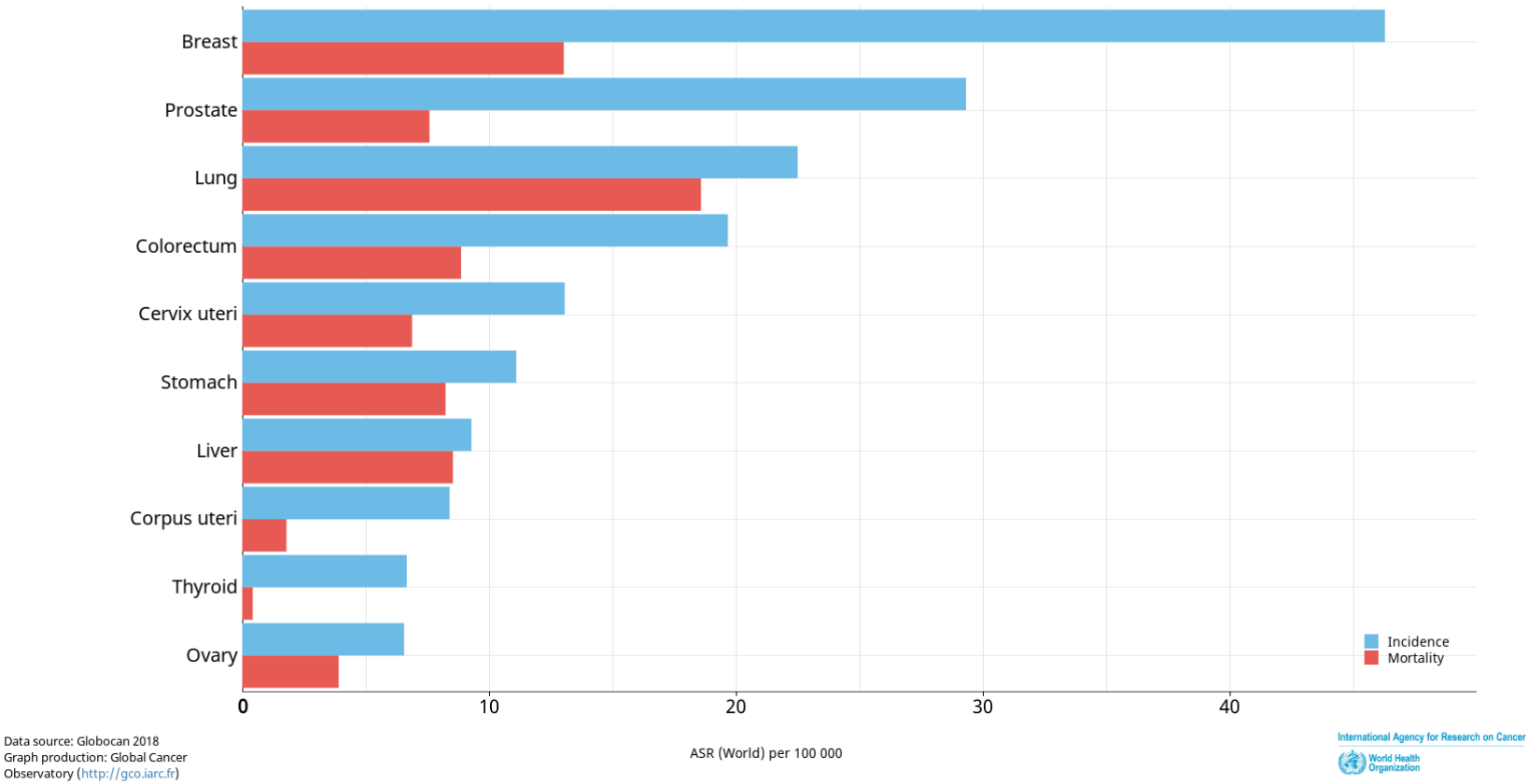
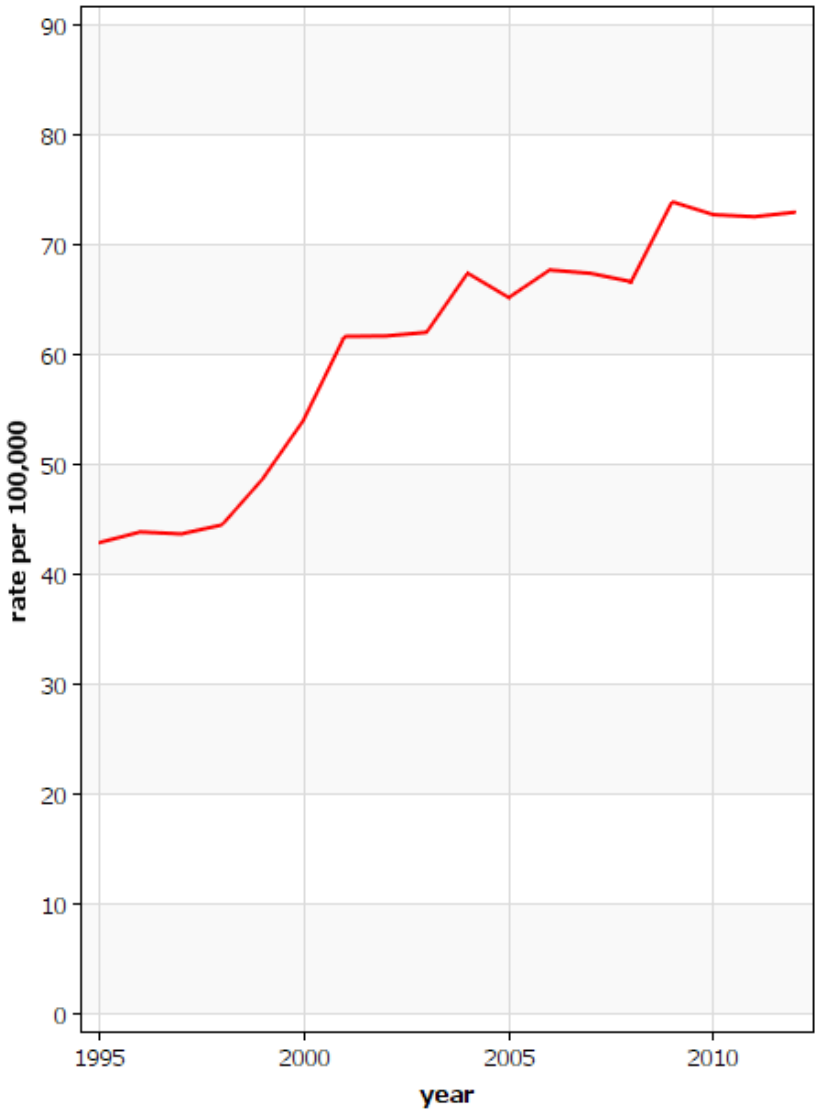


Figure 1. 2: UK incidence rate for prostate cancer from 1995-2012, age-standardised to a global population

Reproduced from the International Agency for Research on Cancer [1]. Year given on x-axis and incidence rate (per 100,000 people) given on y-axis.



1.3 Histopathological features of prostate cancer

To make a diagnosis of prostate cancer, samples of tissue are taken from the prostate and analysed by a pathologist using light microscopy. The three classical hallmarks of prostate cancer include loss of basal cells, nuclear atypia and infiltrative small glands or large irregular cribriform glands [8]. Prostate cancer typically develops from acinar or ductal epithelial cells giving rise to an

adenocarcinoma, though rarer forms exist, such as squamous or neuroendocrine cancers. Donald Gleason developed a grading system to assess the differentiation of the glandular cells, assigning a Gleason pattern of 1-5, where the higher the Gleason pattern, the more poorly differentiated the tissue and the more aggressive the cancer [9]. The original Gleason grading system has undergone a number of modifications, agreed at the International Society of Urological Pathology (ISUP) 2005 and 2014 consensus meetings [10, 11]. Notable recommendations include that Gleason pattern 1 and 2 should no longer be made on biopsy and the recommendation of use of a Gleason grade grouping system that ranges from 1-5, which may correlate better with prognosis and may be more reassuring to patients [11].

Table 1. 1: Correlation of proposed ISUP Gleason grade group with the modified Gleason grading system

Information derived from [11]

ISUP Gleason Grade Group	Modified Gleason grading system
1	3 + 3 = 6
2	3 + 4 = 7
3	4 + 3 = 7
4	4 + 4 / 3 + 5 / 5 + 3 = 8
5	4 + 5 / 5 + 4 / 5 + 5 = 9 – 10

1.4 History of prostate cancer diagnosis

The methods used to obtain prostate tissue for the diagnosis of prostate cancer have evolved over time. Originally in 1937, Astraldi reported the use of finger-guided biopsy in men with an abnormal digital rectal examination. The discovery of prostate specific antigen (PSA), a 33KDa serine protease produced mainly by prostatic epithelial cells, has changed the way that we diagnose prostate cancer today. It was found to be present in higher quantities in those with prostate cancer tissue than normal tissue [12] and finding a PSA value above what one might expect for a man of that age is the most common way for men to present to a Urologist with suspected prostate cancer. With the advent of ultrasound, the transrectal ultrasound guided prostate biopsy was introduced in 1989 [13]. This

allowed visualisation of the prostate and its anatomical landmarks and needles could be seen entering the prostate. The original schema was a 6-core biopsy from the apex, mid-gland and base of each prostate lobe. The adaptation of this to a 10-12 core schema then followed which was demonstrated to increase the amount of cancer identified [14, 15]. Further biopsies were added to the 12 core TRUS biopsy, though cancer detection rates did not increase significantly [16] and in most centres 10-12 core TRUS biopsy is currently the standard initial diagnostic test for men with suspected prostate cancer. TRUS biopsy is a procedure can be done routinely under local anaesthetic in an outpatient setting and thus is feasible and practical at most urological centres.

1.5 Clinical significance of prostate cancer

The principle of needle biopsy is to get samples of prostatic tissue to determine the presence or absence of cancer and if present to characterise the underlying burden of cancer for this patient to allow an appropriate management plan to be formulated. A clinically significant prostate cancer is one that is likely to affect a man in his lifetime by causing morbidity or mortality and thus one that potentially would benefit from treatment. However, there is no consensus on the exact definition of clinical significance. Important patient factors include the patient's performance status and their likelihood of dying from other comorbidities. Cancer-specific factors are thought to be related to features such as the Gleason grade and volume of disease. Gleason grade is one of the strongest predictors of biochemical recurrence following radical prostate cancer treatment with a Gleason grade group of 5 having a hazard ratio of 11.7 compared to a Gleason grade group of 1 [17]. Gleason grade and tumour volume have both been demonstrated to be independent predictors of biochemical recurrence [18].

1.6 Errors associated with TRUS biopsy

As one cannot visualise easily suspicious areas on ultrasound, the biopsy cores during a TRUS biopsy are directed at the peripheral zone at the base, mid gland and apex, where cancer is most likely to be present. This procedure is associated with a number of diagnostic errors including the under-diagnosis of clinically important cancer, the over-diagnosis of clinically unimportant cancer and

misclassification of disease [19, 20]. Anterior, midline and apical tumours can be missed systematically due to the needle trajectory. As a result, TRUS-biopsy has been criticised as an approach for the diagnosis of prostate cancer. Further limitations include the risk of sepsis with hospital admission which is in the region of 1-3% [21]. This results from the translocation of faecal and gut bacteria from the rectum into the prostate.

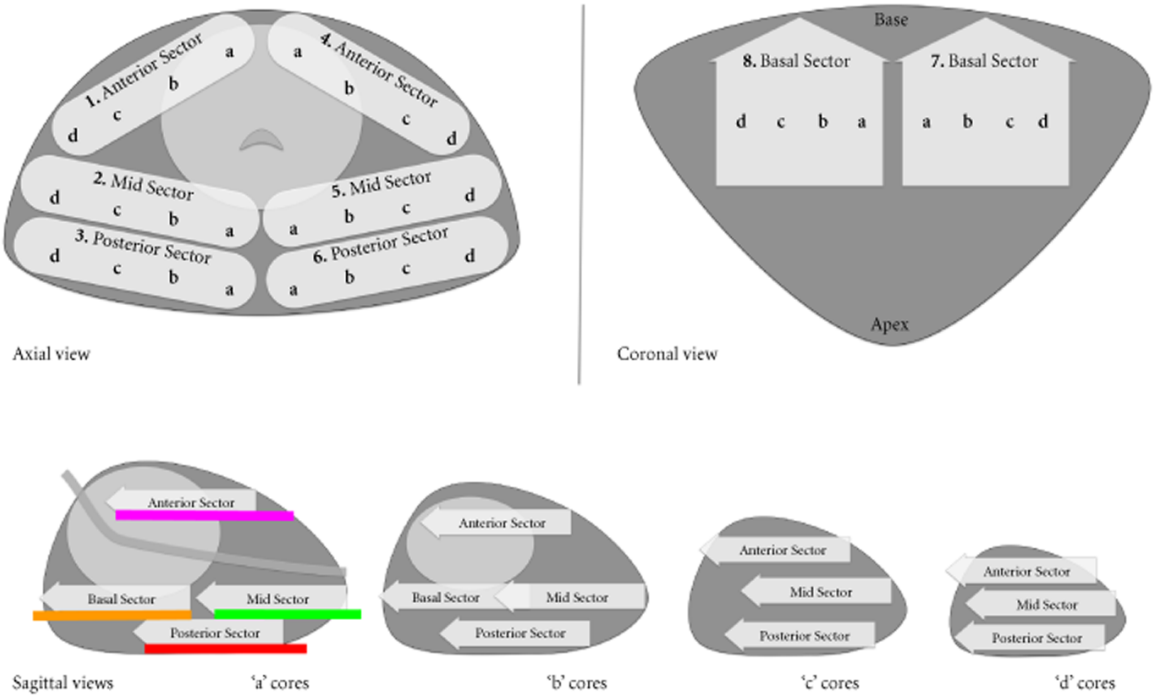
1.7 Transperineal prostate biopsy

Alternatives diagnostic approaches that have developed to mitigate some of these problems include transperineal prostate (TP) biopsy. The transperineal approach for prostate biopsy with ultrasound guidance was first reported by Holm in 1981 [22], though the more detailed approach was formalised by Onik as transperineal mapping prostate biopsy [23], where biopsy cores are taken every 5mm along a brachytherapy grid under sedation or general anaesthetic to give a detailed representation of cancer burden [24]. This technique has been shown to increase significant cancer detection and has a much lower sepsis rate as biopsies are taken through the perineum. However, it is typically associated with high rates of urinary retention of up to 24% and erectile dysfunction as measured by a reduction in International Index of Erectile Function-15 scores of around 20% [25]. Hypotheses to explain urinary retention include gland swelling causing bladder outflow obstruction and the anaesthetic affecting bladder function. Erectile dysfunction has been hypothesised to result from swelling of the prostate on the neurovascular bundle causing a temporary neuropraxia [26].

As there is no consensus on the optimal way of performing TP biopsy, there are a range of modifications to transperineal mapping biopsy that have been developed. As well as differing in their sampling density, these modifications often avoid sampling areas where significant cancer is thought to be less frequently found, in order to reduce patient burden. One such commonly practiced method is transperineal sector biopsy, which takes biopsy cores from the anterior, middle and posterior parts of the gland, from lateral to medial, with additional basal biopsies in the presence of a larger prostate (Figure 1. 3) [27].

Figure 1. 3: Transperineal sector biopsy schema

Reproduced with permission from [27]. Biopsy cores are taken from the anterior, middle and posterior prostate, from the lateral part of the prostate extending medially (d-a). Additional basal biopsies are taken if the prostate is greater than 30cc and greater than 4cm in length.



This approach spares the transition zone which reduces the morbidity of the procedure. One of the limitations with TP biopsy has traditionally been the need for an anaesthetist and a theatre environment which makes the procedure more resource-consuming compared to TRUS biopsy. However, in recent years local anaesthetic TP biopsy has become increasingly used, which allows the more detailed approach of TP biopsy to be applied in an outpatient based setting [28]. Despite these potential advantages, the most commonly carried out test for prostate cancer around the world still remains TRUS biopsy due to its practicality and availability. For the purposes of this thesis, the term "systematic biopsy" will be used to refer to either TRUS biopsy or TP biopsy.

1.8 Challenges in prostate cancer research

Prostate cancer treatment has a narrow therapeutic margin. Compared to the high incidence of disease, a much lower proportion of men die from their disease

(Figure 1. 1). A large proportion of cancer is clinically insignificant and unlikely to cause harm to patients. The introduction of PSA as a triage test has led to this problem as PSA poorly discriminates between men with significant and insignificant cancer at the PSA ranges commonly seen in men with suspected localised disease [29]. The ideal diagnostic test would identify as much clinically significant cancer as possible, with the fewest biopsy cores, thus having a low side effect profile and causing the least harm to patients whilst identifying those men who would benefit from treatment. In addition, the ideal test would avoid the diagnosis of clinically insignificant cancer which may not benefit from treatment. Reducing overtreatment of clinically insignificant disease is a major unmet need in prostate cancer research. Three major randomized trials examining the effect of PSA screening on prostate cancer-specific survival have been carried out (Table 1. 2).

Table 1. 2 A summary of the key features of the randomized trials evaluating PSA screening to reduce prostate cancer-specific mortality

PCLO = Prostate, Lung, Colorectal and Ovarian Study, ERSPC = European Randomized Study of Screening for Prostate Cancer, CAP = Cluster Randomized Trial of PSA Testing for Prostate Cancer

Study	Population studied	Intervention arm	Control arm	Main findings
PCLO 1993-2001[30]	76,685 men aged 55-74	Annual PSA testing for 6 years and annual DRE testing for 4 years. Positive test: PSA > 4ng/ml or abnormal DRE	Usual care	No difference in prostate cancer-specific mortality at 13 years (RR 1.09 [95% CI 0.87-1.36])
ERSPC 1991-2005[31]	182,160 men aged 50-74	4-yearly PSA testing in most centres. Positive test: PSA > 3ng/ml	Usual Care	Reduction in prostate cancer-specific mortality at 13 years (RR 0.79 [95% CI 0.69–0.91])
CAP 2001-2009[32]	419,582 men aged 50-69	Single invitation for PSA testing. Positive test: PSA > 3ng/ml	Usual care	No difference in prostate cancer-specific mortality at 10 years (RR 0.96 [95% CI 0.85-1.08]

Though the Prostate, Lung, Colorectal and Ovarian (PCLO) trial did not identify any difference in prostate cancer-specific survival it was heavily criticised because of a high rate of contamination from men in the unscreened arm who

actually ended up having PSA screening, which was 40% in the first year of screening [30]. The Cluster Randomized Trial of PSA Testing for Prostate Cancer (CAP) trial evaluated a one-off invitation for a single PSA test and this approach also did now show a survival improvement [32]. Contamination rates in the CAP trial were estimated at 10-15%. On the other hand, the European Randomized Study of Screening for Prostate Cancer (ERSPC) did show a modest improvement in prostate-cancer specific survival at 13 years demonstrating that 1 prostate cancer death would be averted per 781 men invited for screening [31]. However, the authors correctly point out the substantial over-diagnosis and overtreatment resulting from the PSA screening programme and recommended careful consideration of the risks and benefits on whether or not routine PSA population screening should be carried out.

The outcomes from men identified by a PSA screening are important to examine in more detail. The Prostate Testing for Cancer and Treatment (PROTECT) randomized study demonstrated that for cancer diagnosed by a PSA driven, TRUS-biopsy diagnosed pathway, radical treatment (with radical prostatectomy or radiotherapy) does not offer a prostate cancer-specific reduction in mortality over active surveillance at 10 years [33]. The Prostate cancer Intervention Versus Observation Trial (PIVOT) showed that radical prostatectomy did not lead to an improved survival over observation and this was particularly evident in the men with low risk disease [34]. Thus, treating low risk prostate cancer with radical treatment can lead to side effects such erectile dysfunction, urinary incontinence and bowel toxicity [35] without offering a survival benefit.

Some of the criticism of these studies was that the proportion of men with low risk disease, for example Gleason grade 3+3, was high, meaning that treatment in these men would not likely lead to benefit anyway and would reduce the power of the study to show a difference in prostate cancer-specific survival for men with intermediate and high-risk disease. Certainly, following the PIVOT study, there has been a move away from treating low risk disease. Initial subgroup analysis of the patients with high and intermediate risk disease in PIVOT showed that treatment may lead to an overall improvement in survival and thus this is the group of patients that stand potentially to benefit the most. However, criticism of

PIVOT surrounded the baseline comorbidity of the patient population who were an older and more comorbid sample and thus treatment was less likely to demonstrate benefit due to competing risk of mortality. In PROTECT, although no overall difference in cancer-specific survival was demonstrated between surgery, radiotherapy or active surveillance, men placed on active surveillance did have a higher rate of metastasis and one could hypothesis that with greater follow up time, men in these group may fare worse, providing they do not die from other comorbidity. Proponents of active surveillance would highlight that men risk stratified with more modern approaches including prostate MRI may lead to more appropriate selection of men for active surveillance, thus perhaps men today may not experience the same outcomes.

1.9 Adjuncts and alternatives to PSA in the diagnostic pathway

Given the limitations of PSA test in identifying men who are likely to harbour significant cancer and benefit from treatment, research efforts have focussed on identifying modifications or alternatives to PSA.

I. Free: total PSA ratio. PSA is primarily bound to proteins in the blood, though a proportion is free, unbound to protein. Studies have shown that in men presenting with a total PSA of 4-10ng/ml, the risk of cancer is higher in men with lower free:total PSA ratios. Particularly, if a free:total PSA ratio of greater than 25% was used as a threshold for avoiding biopsy, this would have allowed the safe avoidance of 20% of unnecessary prostate biopsies [36, 37].
II. PSA Velocity. The rate of change of PSA over time was also demonstrated to differentiate between those with and without prostate cancer with a PSA velocity of 0.75mcg/L/year being more likely to predict those developing prostate cancer [38].
III. PSA Density. Since PSA is produced by benign epithelial tissue, in general, the larger the prostate, the higher the PSA without necessarily having a higher risk of cancer. A measure therefore to take into account the size of the prostate when deciding whether a man's PSA value is raised is intuitive. PSA Density is calculated by dividing the PSA by the

volume of the prostate. High PSA densities are more likely to be related to significant prostate cancer with a PSA Density of greater than 0.15ng/ml/ml more likely to predict significant cancer [39].

IV. Other PSA derivatives. The prostate health index (PHI) is based on a formula combining the PSA derivatives: PSA, free PSA, and pro2PSA. The higher the PHI value, the more likely there is to be significant prostate cancer. PHI may help avoid biopsy in a proportion of men. A threshold value of 27.6 was shown to have potential to avoid 16% of unnecessary prostate biopsy [40]. The Four-Kallikrein (4K) panel is also based on PSA derivatives, namely total PSA, free PSA, intact PSA, and human kallikrein-2. The results are used in an algorithm together with the patient's age, prior biopsy status and digital rectal examination finding to produce a 4K test result giving a risk for aggressive prostate cancer. The higher the 4K score, the higher the risk of clinically significant cancer. The 4K score has been shown to improve the ability to predict prostate cancer and may be able to reduce unnecessary biopsies [41].

V. Urinary biomarkers. Prostate cancer gene 3 (PCA3) and SelectMDX tests are based on mRNA biomarkers, measured in the urine following digital rectal examination. PCA3 is a non-coding mRNA whereas the SelectMDX test measures HOXC6 and DLX1 mRNA. Both biomarkers have demonstrated value in identifying men with clinically significant cancer [42, 43].

Despite some of these adjuncts and alternatives to PSA showing promise, none have replaced PSA and in clinical practice PSA testing is still the main way in which men present to a Urologist with clinical suspicion of prostate cancer. Thus, due to its previously discussed limitations, there is a need to develop other adjuncts to PSA to help identify the group of patients who would benefit most from further investigation and treatment.

1.10 Emerging role of prostate MRI

Over the last 15 years, the role of prostate MRI in prostate cancer diagnosis has become increasingly important. Traditionally the value of prostate MRI was

limited as biopsies were often done before the MRI, which caused artefact on the scan, and because the imaging was not typically optimised for prostate cancer diagnosis [44]. The addition of a range of sequences lead to the MRI being termed multiparametric MRI, which has shown a much better performance in detecting clinically significant cancer [45].

MRI works by creating a magnetic field around the patient, which excites protons in tissue containing water, causing them to align in a particular fashion. A radiofrequency pulse can be applied causing the protons to move out of alignment. As the pulse is stopped and the protons drop to lower energy states they emit a radiofrequency signal which is measured by a receiving coil and interpreted as an MRI signal. There are a number of different types of anatomical and functional sequences relevant to prostate MRI:

I. T2-weighted imaging (T2). This is one of the most important sequences to demonstrate the detailed anatomy of the prostate. This allows identification and differentiation between peripheral zone, transition zone, anterior fibromuscular stroma, urethra, seminal vesicles, urethra, prostate capsule and demonstrates the relationship of areas suspicious for prostate cancer to these structures. Cancer in the peripheral zone and transition zone have a low T2-signal (appears as a dark area on the MRI scan).

II. Diffusion weighted imaging (DWI). This functional sequence demonstrates the diffusion of water molecules throughout the tissue. Densely packed tissue such as that seen in cancerous tissue is more likely to demonstrate restricted diffusion (appears as a bright area on the scan). DWI is captured over a range of magnetic gradient strengths, known as b-values. A particularly important b-value image is the high b-value image which is very useful in identifying suspicious areas. An artificially generated sequence, called the apparent diffusion coefficient (ADC) map, is created from all of the b-value images taken. Like the images from which it is composed, the ADC map therefore gives an estimation of how easily water diffuses through tissues. In the ADC map, suspicious areas of the prostate appear as a dark area on the scan.

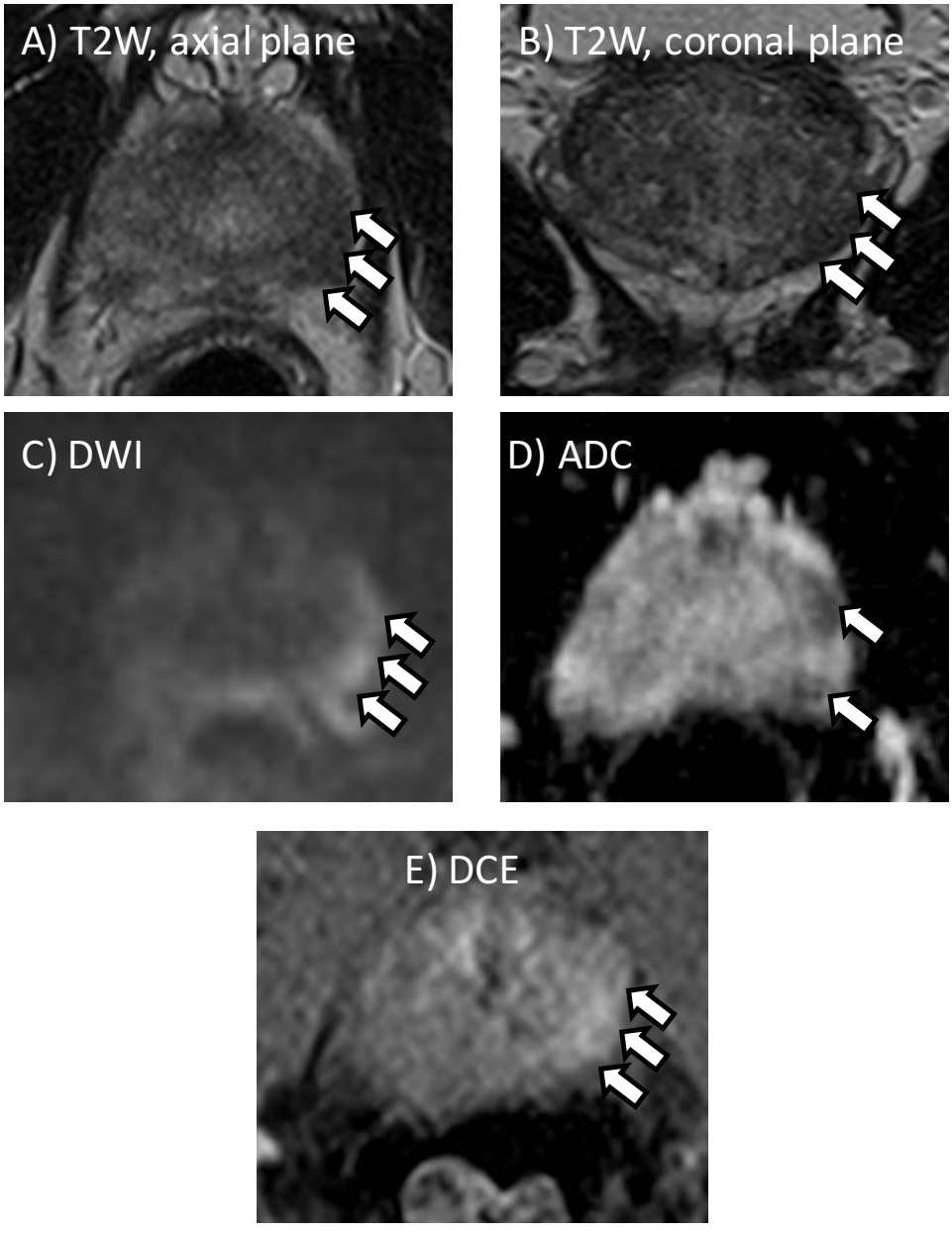
III. Dynamic contrast enhancement (DCE). Baseline T1-weighted images are taken prior to contrast being administered, which allow one to assess for the presence of prior biopsy haemorrhage. Then intravenous gadolinium-based contrast is injected and a series of images are taken over time to evaluate the prostate as contrast reaches it. The early enhancement phase is the most useful in identifying prostate cancer. Cancer tends to enhance (show up as a bright area on the MRI scan) on the early enhancement phase as the neovascularisation caused by angiogenesis by the cancer causes more contrast to enter the cancer. Often the contrast can wash out quickly in the presence of cancer.

IV. Magnetic resonance spectroscopy (MRS). This imaging sequence determines metabolic information about the prostate tissue. It determines the ratio of metabolites in the cells and extra-cellular space. Prostate cancer has lower levels of citrate and higher levels of choline and creatine than benign tissue and the MRI signal allows this differentiation to be made. It has gone out of fashion as it has shown limited additional value over DWI and further, dedicated software is typically needed to interpret it.

A suspicious area on multiparametric is demonstrated in Figure 1. 4. The different sequences carried out are interpreted together in order to look for the presence or absence of areas suspicious for clinically significant prostate cancer.

Figure 1. 4: A multiparametric MRI demonstrating an area suspicious for significant cancer

T2-weighted imaging in axial (A) and coronal (B) planes. An area of low T2, appearing "dark" in relation to surrounding area, marked by white arrows, is suspicious for significant cancer. It is located in the left apex to mid-gland at 2-5 o' clock. This area shows restricted diffusion on diffusion weighted imaging (C), appearing "white" in relation to surrounding area and shows a high ADC value on the ADC imaging (D), appearing "dark" in relation to surrounding areas. Early contrast enhanced imaging (E) reveals enhancement of the same area, appearing "white" in relation to the surrounding area. This area was scored as being highly suspicious (5/5 on Likert scale) and after targeted biopsy revealed Gleason 4+3 prostate cancer.



Standardisation of multiparametric MRI conduct and reporting have also helped to improve the quality of prostate MRI. The score of suspicion of prostate cancer is typically produced on a 1-5 Likert scale of suspicion (Table 1. 3) based on the radiologist's impression of the likelihood of significant cancer being present.

Table 1. 3: Likert scale for suspicion of prostate cancer

Table created from data within [46].

Likert score	Meaning
1	Highly unlikely to be significant prostate cancer
2	Unlikely to be significant prostate cancer
3	Equivocal for the presence of significant prostate cancer
4	Likely to be significant for prostate cancer
5	Highly likely to be significant prostate cancer

The PI-RADS v1 and v2 guidelines are a set of guidelines by which these scores can be derived [47, 48]. They allow communication between professionals using prostate MRI on the risk of cancer in a way that is understood by people in different settings. Although there is some debate of whether a Likert score without these rules or PI-RADS scores with these rules better predicts prostate cancer, what is more certain is that incorporating MRI into the diagnostic pathway improves the detection of clinically significant cancer [24, 49].

Using the main sequences of T2, DWI and DCE, the Prostate MRI Imaging Study (PROMIS) showed that MRI was superior to TRUS biopsy in the detection of clinically significant prostate cancer with a sensitivity of 93% [95% CI 88-96%] for MRI vs 48% [95% CI 42-55%] for TRUS biopsy [24] (Table 1. 4). A summary of the key design features of the PROMIS study is given in Figure 1. 5.

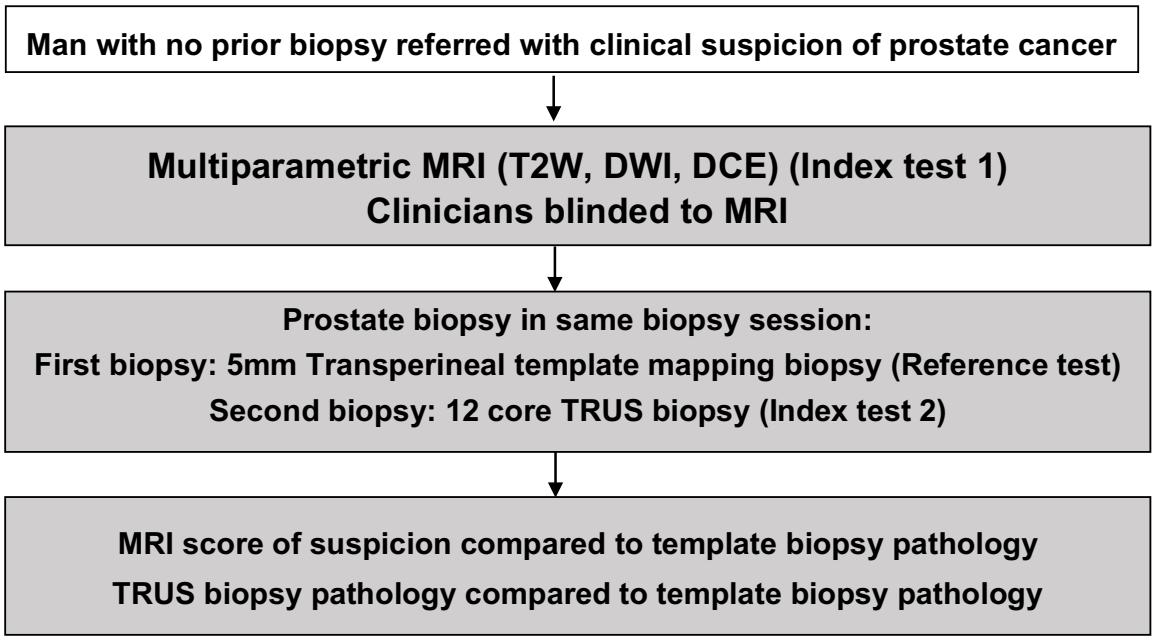
Table 1. 4: Diagnostic performance of MRI versus TRUS biopsy in the detection of clinically significant cancer

Adapted from [24]. MRI = Multiparametric MRI with T2-weighted, diffusion-weighted and dynamic contrast enhanced sequences. Clinically significant cancer from primary study definition given by any Gleason score 4+3 or greater and/or maximum cancer core length of 6mm. Figures in brackets are 95% confidence intervals.

	Sensitivity	Specificity	Positive predictive value	Negative predictive value
TRUS biopsy	48 [42-55]	96 [94-98]	90 [83-94]	74 [69-78]
MRI	93 [88-96]	41 [36-46]	51 [46-56]	89 [83-94]
Test ratio	0.52 [0.45-0.60]	2.34 [2.08-2.68]	8.2 [4.7-14.3]	0.34 [0.21-0.55]
p-value	p<0.0001	p<0.0001	p<0.0001	p<0.0001

Figure 1. 5: PROMIS study schema

Adapted from [24]. T2W = T2-weighted, DWI = Diffusion weighted imaging, DCE = Dynamic contrast enhanced imaging



Men underwent pre-biopsy multiparametric MRI followed by a general anaesthetic transperineal template mapping biopsy followed by a TRUS-biopsy in the same biopsy session. The biopsy operators were blinded to the MRI findings. This study highlighted that compared to standard of care of TRUS biopsy,

multiparametric MRI identified more men with significant disease who would benefit from treatment and the superior negative predictive value highlighted the potential to use MRI as a triage test to avoid prostate biopsy. PROMIS is a landmark study consolidating the value of pre-biopsy multi-parametric MRI.

However, the PROMIS study was an explanatory trial, showing how good MRI was but it didn't investigate how we should use the information in men with suspected cancer, given biopsy operators were blinded to the MRI information. In addition, the detailed transperineal biopsy, carried out in the study, sampling the prostate every 5mm throughout its entirety, is not feasible in routine clinical practice. In PROMIS, a man with a prostate of 50cc size would typically get 50 biopsies which is a very intensive sampling regime. Further, a primary definition for clinically significant cancer of Gleason grade 4+3 and/or maximum cancer core length of 6mm or greater was used, and it could be argued that men with disease less severe than this would harbour significant cancer and be eligible for treatment.

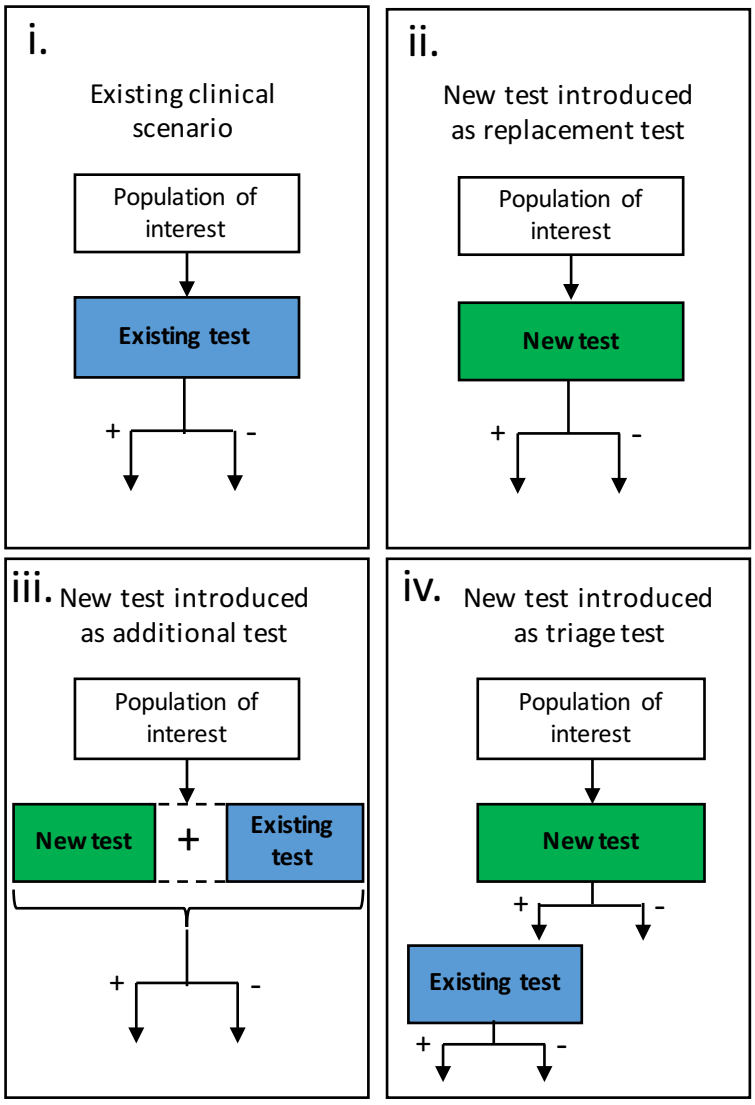
When using a less strict definition of clinically significant cancer of Gleason grade 3+4 and/or maximum cancer core length of 4mm or greater, the performance of MRI was still better than TRUS biopsy, though 28% percent of men with a negative MRI would be missed with significant cancer. This raised concerns over whether a negative MRI should be used to avoid a biopsy given the proportion of men missed. Despite this, a fact not commonly discussed was that the MRI missed no Gleason 4+3 or worse cases, which are the cases that are known to be ones that would benefit the most from treatment. All of the misses were due to men with lower Gleason grade cancer (3+3 or 3+4) crossing the threshold value for length of cancer in a single core being greater than 4mm. Certainly though, PROMIS gave us invaluable high-quality evidence supporting an MRI-influenced pathway, but leaving room for further research on how to use that MRI information.

1.11 MRI-targeted biopsy

In diagnostic test evaluation research methodology, there are a range of possible roles for a new diagnostic test. Tests can be a triage test, replacement test or an additional test to standard of care (Figure 1. 6).

Figure 1. 6: Possible roles for a new diagnostic test

Adapted, with permission, from [50]. (i) shows the current clinical situation where the existing test is applied to a population of interest. (ii) demonstrates when a new test is proposed to replace the existing test. (iii) demonstrated when the new test is used together with the existing test as an additional test to ascertain disease status. (iv) demonstrates when the new test is applied first and the result used to decide whether or not to carry out the existing test.



A key attraction of prostate MRI is its potential role as a triage test in men with raised PSA or abnormal digital rectal examination. If the MRI is non-suspicious there is the possibility of avoiding a biopsy and if the MRI is suspicious, men can undergo a biopsy. In addition, MRI information can be used to influence how that biopsy is carried out, which is termed MRI-targeted biopsy (MRI-TB). In this procedure, biopsy cores are concentrated on areas of the prostate suspicious on MRI and in doing so, it is hoped that the errors associated with TRUS biopsy can be mitigated. Specifically, cores may be more likely to sample representative parts of the tumours thus giving better risk stratification for the patient which may lead to more appropriate management decisions. In addition, it may allow one to avoid the overdetection of clinically insignificant cancer as MRI suspicious areas are more likely to harbour clinically significant disease.

MRI-TB can be used as an additional test to systematic biopsy or can be used as a replacement test to systematic biopsy. Advantages of using MRI-TB as an additional test include that the greatest amount of cancer is likely to be identified with more sampling of the prostate. However, disadvantages include that more men with clinically insignificant cancer will be identified as the systematic biopsy test is still carried out. This means that the problem of overtreatment would not be mitigated by this approach. Advantages of using MRI-TB biopsy as a replacement test to systematic biopsy would be the identification of a similar amount of clinically significant cancer, whilst avoiding the diagnosis of clinically insignificant cancer. Thus, the focus of this thesis is to evaluate the role of MRI-TB as a replacement test to systematic biopsy in men with suspected prostate cancer based on raised PSA or abnormal digital rectal examination.

1.12 Existing knowledge on MRI-targeted biopsy

At the time of commencing this body of work, a systematic review summarised the key literature in this field [51]. Only one single centre study by Haffner [52] met the optimal criteria required to evaluate the role of MRI-TB as a replacement test to systematic biopsy. The optimal criteria being a study in which men with clinical suspicion of prostate cancer based on raised PSA or abnormal digital rectal examination underwent both MRI-TB and systematic biopsy and the

histopathological results for each of the comprising biopsies being reported separately. This study looked at 555 consecutive men who underwent pre-biopsy MRI on a 1.5 Tesla MRI machine, using T2-weighted and dynamic contrast enhanced imaging [52]. After MRI, all men underwent 10-12 core transrectal prostate biopsy and in addition 2 cores targeted to areas of the prostate that looked suspicious on MRI. For significant prostate cancer detection, sensitivity, specificity and accuracy of targeted biopsies were 0.95, 1.0 and 0.98. For systematic biopsies, these values were 0.95, 0.83 and 0.88, respectively. This showed that the accuracy of MRI-targeted biopsy was higher than systematic biopsies for the detection of clinically significant cancer.

Though the systematic review highlighted that the reporting quality of MRI-targeted biopsy studies was poor, which limited the ability to evaluate the technique (see Chapter 3) [51], it did make several other key observations about the MRI-TB approach which influenced the approach taken in the current body of research work. First, in men with clinical suspicion of prostate cancer, 63-95% of men undergoing MRI had a visible MRI lesion identified. This has implications in that if an MRI-targeted alone biopsy approach were to be taken, significant cancer can only be identified in those with an MRI lesion undergoing MRI-TB. Should MRI-TB be used as part of a process where MRI itself was used as a triage test, then this highlights the proportion of patients in whom it could be suggested that a biopsy should be avoided. Second, that 42-70% of men undergoing targeted biopsy in the presence of an MRI lesion had a biopsy positive for cancer. This gives an indication of the positive predictive value of a targeted biopsy in men with an MRI lesion, which can provide a useful reference point as a comparison to systematic biopsy. Third, that only 2.3% of men with a non-suspicious MRI would have clinically significant prostate cancer missed if they did not have a biopsy. This has important implications in allowing men with non-suspicious MRI to safely avoid a prostate biopsy.

In summary, it is clear that further work on the role of MRI-TB of the prostate would be worthwhile, given the promise of early reports in this field. However, further data corroborating these early findings would be needed and a number of limitations in the existing literature would need to be overcome in order to

evaluate MRI-TB as an alternative to systematic biopsy for the diagnosis of prostate cancer.

Chapter 2 MRI-targeted biopsy compared to systematic biopsy in a single institution setting

The findings from the work in this chapter have been published in *The Journal of Urology* [53].

2.1 Introduction

The potential limitations of TRUS biopsy as a diagnostic test due to random and systematic error associated with it have been discussed (Section 1.6). As a result, some institutions use transperineal template prostate biopsy as the standard diagnostic technique in men with suspected prostate cancer. Resources required are greater and centres currently doing this are commonly tertiary academic centres. Another reason for choosing transperineal template prostate biopsy rather than TRUS biopsy as the standard diagnostic approach can relate to what treatments are offered at the institution. Radical whole gland treatment, for example with radical prostatectomy or radiotherapy, is typically standard of care for the treatment of localised prostate cancer.

Focal therapy is a more recently proposed treatment which has a principle of treating part of the prostate containing the cancer rather than the whole prostate. The hope is that the oncological outcomes can be preserved whilst functional outcomes such as urinary incontinence and erectile dysfunction can be minimised. Where focal treatments are first introduced into a service, a detailed biopsy assessment of the whole prostate is classically carried out in order to be sure that a patient will be suitable for focal treatment.

Our institution at the time of this study had initiated a focal therapy program and transperineal template biopsy was the standard diagnostic test offered to patients. With the majority of our patients receiving pre-biopsy MRI, this set up offered an opportunity to carry out transperineal MRI-targeted biopsies of the prostate and systematic transperineal template biopsies in the same patient. A study design where each man undergoes both biopsy tests in the same biopsy session allows the relative merits of each of the tests to be assessed. This study

design, often referred to as a paired cohort, is the classical study design adopted in the evaluation of MRI-targeted biopsy. As each man serves as his own control, such a design has good power to detect a difference in the proportion of men identified with cancer by each procedure.

Indeed, though burdensome, it is thought that a transperineal template prostate biopsy is one of the most detailed diagnostic tests that can be carried out in a man with suspected prostate cancer. Thus, if MRI-targeted biopsy performed well against a very detailed test such as transperineal template prostate biopsy, then this would provide evidence supporting an MRI-targeted only approach. The aim of this study was to evaluate how much clinically significant and clinically insignificant cancer was detected by MRI-targeted biopsy compared to transperineal template biopsy in order to evaluate whether an MRI-targeted alone approach was feasible. I hypothesised that MRI-targeted biopsy would detect a similar amount of clinically significant cancer as transperineal template prostate biopsy but less clinically insignificant cancer.

2.2 Methods

2.2.1 Study design

This was a retrospective evaluation of consecutive men undergoing pre-biopsy MRI, transperineal template biopsy and MRI-targeted biopsy as part of routine care at our institution between the dates of February 2010 and March 2012.

The inclusion criteria were all men in the time period undergoing prostate biopsy for suspicion of clinically significant prostate cancer, with raised PSA and/or abnormal digital rectal examination. In order to minimise selection bias, consecutive patients with all backgrounds, regardless of prior biopsy status were included in the study. Patients with prior treatment to the prostate for prostate cancer were excluded.

Ethical exemption applied for this study as per UK Health Research Authority guidelines and the local institutional review board confirmed this.

The study was reported according to standards for reporting of diagnostic accuracy studies (STARD) guidelines.

2.2.2 MRI details

Patients underwent pre-biopsy multiparametric MRI on a 1.5 Tesla Siemens Avanto or 3 Tesla Siemens Verio machine using pelvic phased array body coils, without an endorectal coil. The MRI sequences used were T2-weighted imaging, diffusion weighed imaging and dynamic contrast enhanced sequences, carried out according to guidelines from a European consensus meeting [46]. The details of the MRI protocol are given in Table 2. 1. Following the MRI, this was reported by one of 4 radiologists with up to 10 years of experience in prostate MRI. The radiologist, who was aware of clinical information, would mark on the MRI any suspicious areas scored on the 1-5 Likert scale of suspicion (Table 1. 3) and would provide a prose report. The Urologist would use this information to perform a biopsy on a separate day.

Table 2. 1: MRI protocol

T2 = T2-weighted, DCE = dynamic contrast enhanced images, DWI = Diffusion weighted images, TR = repetition time (milliseconds), TE = echo time (milliseconds), Flip angle (degrees), FOV = field of view; acq = acquisitions; avr = averages

Sequence	TR	TE	Flip angle	Plane	Slice thickness (gap)	Matrix size	FOV, mm	Time for scan
1. T2	5170	92	180	Axial, coronal	3mm (10% gap)	256x 256	180x 180	3m 54s (ax), 4m18s (cor)
2. DCE VIBE fat sat	5.61	2.52	15	axial	3mm (20% gap)	192x 192	260x 260	9m 59s (35 17s acq)
3. DWI (b values: 0, 150, 500, 1000)	2200	Min (<98)	-	axial	5mm	172x 172	260x 260	5m 44s (16 avr)
4. Diffusion (b value 1400)	2200	Min (<98)	-	Axial	5mm	172x 172	320x 320	3m 39s (32 avr)

2.2.3 Biopsy procedures

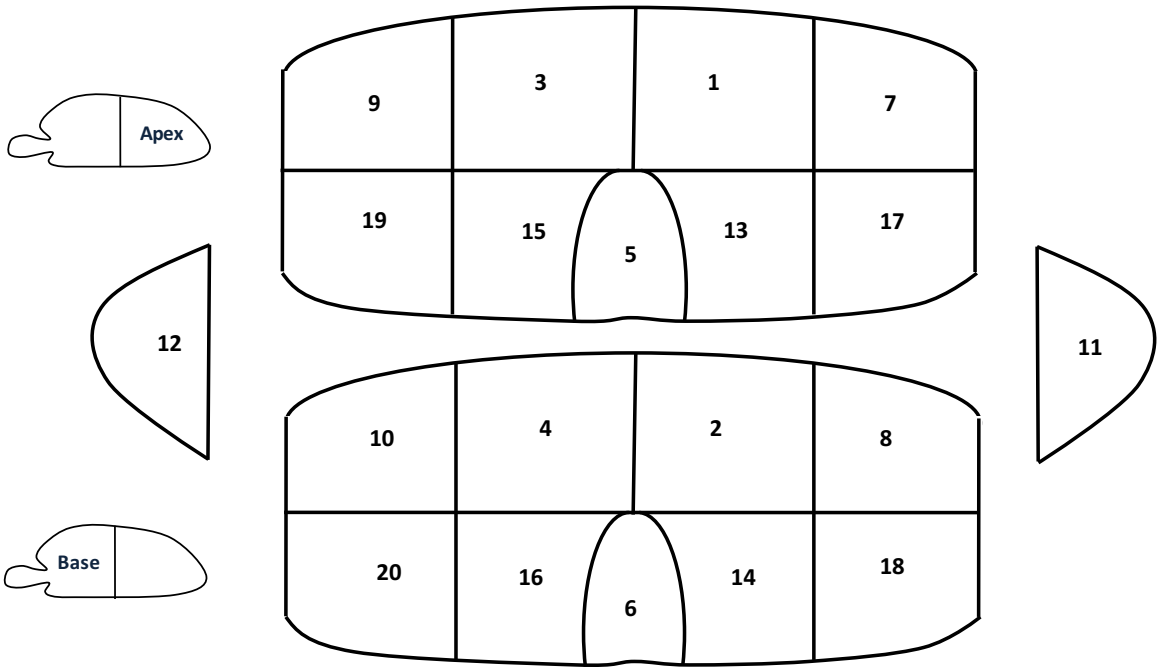
The biopsy procedure was performed in a theatre setting by 1 of 5 urologists with up to 8 years of experience with transperineal template prostate biopsy. Patients would have general anaesthetic, sedation or spinal anaesthesia and have both MRI-targeted and transperineal template prostate biopsy performed in the same biopsy session. The prostate was imaged using a transrectal biplanar ultrasound probe inserted into the rectum. Biopsies were taken from the perineum under ultrasound guidance with assistance from a stepper and a brachytherapy grid. A single operator took both the MRI-targeted and systematic cores. The MRI-targeted cores were taken first in each case. The operator reviewed the MRI on a

screen in theatre, the pictorial diagram and the prose report. They then used their own judgment of where the MRI lesions were in relation to the anatomical landmarks on the MRI (i.e. location of lesion in relation to urethra, apex, base, peripheral zone, transition zone) and related these to the anatomical landmarks on the ultrasound to decide where to place their biopsy needle. This technique is known as visual registration. The operator could see the trajectory of the needle and made a judgement on whether they sampled the suspicious areas appropriately. The number of biopsy cores taken per suspicious area was at the operator's discretion.

After the MRI-targeted biopsies, the operator proceeded to take transperineal template biopsies. Here a 20-sector modified Barzell technique was applied which ensured sampling of the whole prostate at regular intervals throughout the base and apex and anterior and posterior areas, with at least one core from each sector (Figure 2. 1).

Figure 2. 1: 20-sector modified Barzell transperineal template biopsy schema

Reproduced, with permission, from [53]. At least one biopsy core is taken from each of the 20 sectors. The sectors are divided up into apical and basal sectors and anterior and poster sectors.



Modified Barzell Zones

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

Sampling of the whole prostate occurred regardless of whether the areas had been previously sampled in the targeted biopsy, though the biopsy operator was aware of the MRI-findings when performing the systematic biopsy. Biopsy cores from the MRI-targeted and systematic biopsies were stored and labelled separately. An experienced pathologist with 8 years of experience reported the pathological specimens, detailing the Gleason grade and maximum cancer core length, where applicable.

2.2.4 Analysis

A comparison of significant cancer detection was carried out between MRI-targeted and transperineal template biopsy at the patient level. A table of agreement for clinically significant, clinically insignificant and no cancer was created. The proportion of men with significant cancer was determined and differences between the two biopsy tests were calculated and assessed statistically with McNemar's test. The same was applied to differences in insignificant cancer detection for both biopsy tests. A validated primary definition of any Gleason grade 3+4 or greater or maximum cancer core length of 4mm or greater was used as the primary definition of clinically significant cancer in this study. The definition was previously validated by computer simulations of transperineal prostate biopsies into prostates recreated from whole mount prostatectomy specimens [54]. In these simulations, the maximum cancer core length of 4mm identified a tumour volume of 0.2mls on radical prostatectomy and was combined with a Gleason grade of 3+4 to form the primary definition of significant cancer used in the current study. The cancer detection rates were also evaluated for two key subgroups, decided on a priori, which included prior biopsy status and MRI coil strength. Since there is no consensus on the definition of clinically significant cancer, sensitivity analyses for the primary outcome of significant cancer detection were also carried out according to a number of other commonly used definitions including the validated UCL definition 1 (Gleason grade 4+3 or maximum cancer core length or 6mm or greater) and the Harnden definition (Gleason grade 3+4 or maximum cancer core length of 3mm or greater).

Side effects up to 90 days following the biopsy procedure were also recorded from review of the medical records.

2.3 Results

2.3.1 Patient characteristics

In the study period, 235 consecutive men had clinical suspicion of significant prostate cancer and underwent pre-biopsy MRI, MRI-targeted and transperineal

prostate biopsy. Fifty-three were excluded as they had prior treatment for prostate cancer, giving a sample size of 182 men. Of these men, 78 had no prior biopsy, 32 had a previous negative biopsy and 72 men had previous biopsy positive for clinically insignificant cancer (Figure 2. 2). The median PSA was 6.7 and the mean age was 63 (Table 2. 2).

Figure 2. 2: Summary of study flow

A figure summarizing the study flow. T2W = T2-weighted imaging, DWI = diffusion weighted imaging, DCE = dynamic contrast enhanced imaging.

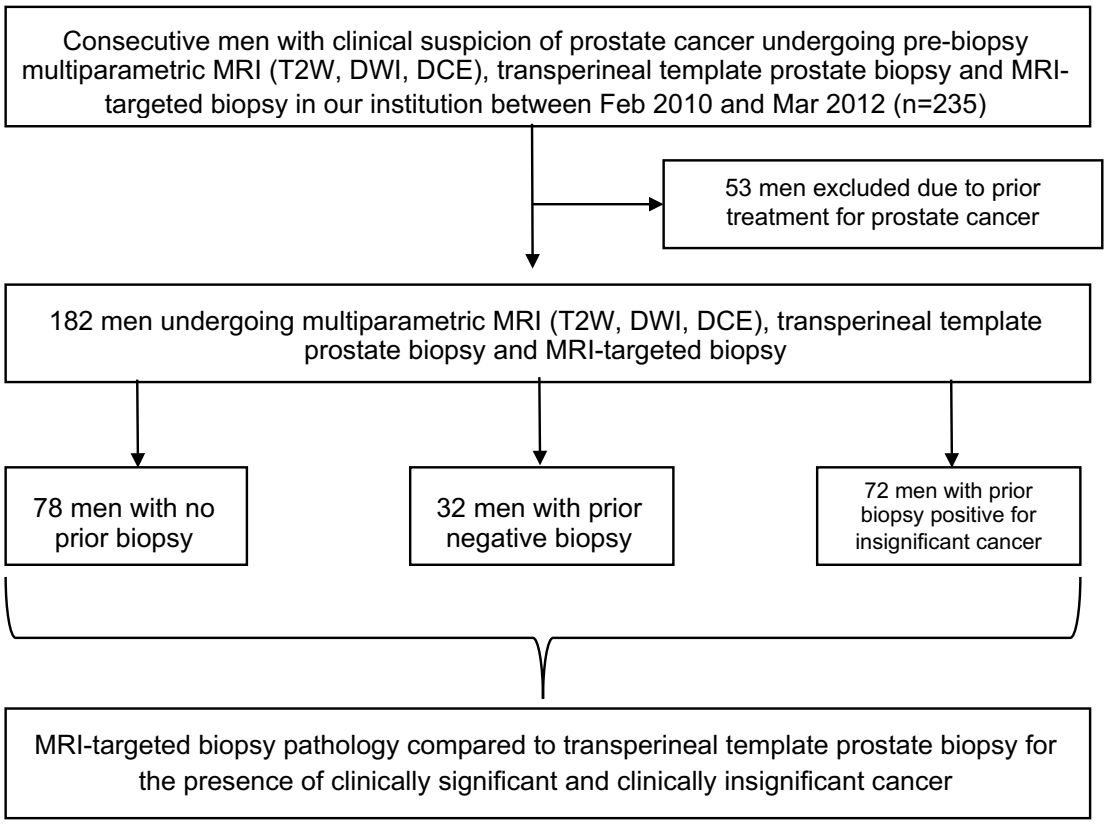


Table 2. 2: Summary of key patient characteristics

Adapted, with permission, from [53].

Characteristic	Value
Number of men included in study population	182
PSA, ng/ml, median (IQR)	6.7 (4.7 – 10.0)
Age, years, mean ±SD	63.3 ± 7.2
Prostate volume, ml, median (IQR)	40.6 (32.0 – 58.0)
MpMRI score ≥ 3 - MpMRI score 3, n (proportion of study population) - MpMRI score 4, n (proportion of study population) - MpMRI score 5, n (proportion of study population)	182 (100%) 45 (25%) 78 (43%) 59 (32%)
1.5 Tesla mpMRIs, n (proportion of study population) 3 Tesla mpMRIs, n (proportion of study population)	115 (63%) 67 (37%)
Time between mpMRI and biopsies, days, median (IQR)	43 (24-69)
Biopsy-naïve men, number (proportion of study population)	78 (43%)
Prior negative biopsy, number (proportion of study population)	32 (18%)
Prior positive biopsy, number (proportion of study population)	72 (40%)

2.3.2 Biopsy characteristics

932 biopsy cores were taken in the MRI-targeted biopsy with a median of 5 cores per patient. 7184 biopsy cores were taken in the systematic biopsy group, with a median of 30 cores per patient. Median sampling density was 0.11 cores/ml of tissue for MRI-targeted biopsy and was 0.88 cores/ml tissue for transperineal template prostate biopsy.

2.3.3 Side effects

There were no men who experienced sepsis, though 5/182 (3%) did experience acute urinary retention and erectile dysfunction. One man (1%) required admission for bladder irrigation for haematuria.

2.3.4 Cancer detection for primary definition

Cancer detection is given in Table 2. 3. 103/182 (57%) of men had clinically significant cancer detected by MRI-targeted biopsy. 113/182 (62%) of men has clinically significant cancer detected by transperineal template prostate biopsy. This difference of 5% [95% CI -2.2-13.1] was not statistically significant (p = 0.17). Systematic biopsy detected 27/113 (24%) cases of significant cancer not detected by MRI-targeted biopsy. MRI-targeted biopsy detected 17/103 (17%) of cases of significant cancer not detected by systematic biopsy.

With regards to clinically insignificant cancer detection, the proportion of men detected by MRI-targeted biopsy was 17/182 (9%). 31/182 (17%) of men has clinically insignificant cancer detected by transperineal template prostate biopsy. This difference of 8% [95% CI 1-14] was statistically significant (p = 0.02).

Table 2. 3: Table of agreement summarising cancer detection by MRI-targeted biopsy and transperineal template prostate biopsy

Adapted, with permission, from [53]. Each number in a box represents 1 patient. Since each man underwent both biopsy tests, they will have a classification for MRI-targeted biopsy and for transperineal template biopsy. The two tests agree where both detect clinically significant cancer (86 men), both detect clinically insignificant cancer (7 men) and both detect no cancer (30 men). They disagree with their classification in all other boxes. For example, Where MRI-targeted biopsy detects clinically significant cancer in 103 men, 7 of these men were classified as having no cancer by template biopsy.

		Template Biopsy			
		Clinically Significant	Clinically Insignificant	No cancer	Totals:
MRI-Targeted Biopsy	Clinically Significant	86	10	7	103
	Clinically Insignificant	9	7	1	17
	No cancer	18	14	30	62
	Totals:	113	31	38	182

2.3.5 Cancer detection by key subgroups

There were no statistically significant differences in the detection rates of MRI-targeted biopsy versus systematic biopsy in 1.5 Tesla coil strength ($p = 0.09$) or in 3 Tesla coil strength ($p = 0.99$). Cancer detection rates by the subgroup of prior biopsy status are given in Table 2. 4 and likewise demonstrate no statistically significant differences in significant cancer detection. The proportion of men with clinically significant cancer for biopsy naïve men for MRI-targeted biopsy vs systematic biopsy was 39/78 (50%) vs 46/59 (59%), respectively, $p = 0.17$; for

men with a prior negative biopsy was 12/32 (38%) vs 12/32 (38%), respectively, p = 0.66; for men with a prior positive biopsy was 52/72 (72%) vs 55/72 (76%), respectively, p = 0.99.

Table 2. 4: Cancer detection classified by prior biopsy status

Reproduced, with permission, from [53].

Characteristic	No prior biopsy	Prior biopsy negative	Prior biopsy positive	All groups
Number of men, n	78	32	72	182
Age, mean ± SD	63.0 ± 7.8	64.2 ± 5.4	63.3 ± 7.2	63.3 ± 7.2
PSA, ng/ml, median (IQR)	6.2 (4.4-8.0)	9.9 (6.8-12.5)	6.4 (4.7-9.9)	6.7 (4.7-10.0)
Prostate volume, mls, median (IQR)	40 (33-56)	57.5 (34-66)	39.5 (31-52)	40.6 (32-58)
Any cancer MRI-TB, n (%) TPB, n (%)	 49 (63%) 56 (72%)	 13 (41%) 19 (59%)	 58 (81%) 69 (96%)	 120 (66%) 144 (79%)
Clinically significant cancer MRI-TB, n (%) TPB, n (%)	 39 (50%) 46 (59%)	 12 (38%) 12 (38%)	 52 (72%) 55 (76%)	 103 (57%) 113 (62%)
Clinically insignificant cancer MRI-TB, n (%) TPB, n (%)	 10 (13%) 10 (13%)	 1 (3%) 7 (22%)	 6 (8%) 14 (19%)	 17 (9%) 31 (17%)

2.3.6 Sensitivity analyses for significant cancer detection

The primary outcome analysis was repeated with a range of different definitions of clinically significant cancer. There were no differences between MRI-targeted biopsy and systematic biopsy when analysing the clinically significant cancer detection by the UCL definition 1 (difference 4% [95% CI -4.7-12.4]) or the Hardnen definition (difference 8% [95% CI 0.6-14.8]), Table 2. 5 and Table 2. 6.

Table 2. 5: Cancer detection using UCL definition 1

Adapted, with permission, from [53]. Sensitivity analysis with definition of clinical significance as any cancer with Gleason grade 4+3 or greater or maximum cancer core length of 6mm or greater. Each number in a box represents 1 patient. Since each man underwent both biopsy tests, they will have a classification for MRI-targeted biopsy and for transperineal template biopsy. The two tests agree where both detect clinically significant cancer (37 men), both detect clinically insignificant cancer (30 men) and both detect no cancer (30 men). They disagree with their classification in all other boxes. For example, where MRI-targeted biopsy detects clinically significant cancer in 61 men, 3 of these men were classified as having no cancer by template biopsy.

		Template Biopsy			
		Clinically Significant	Clinically Insignificant	No cancer	Totals:
MRI-Targeted Biopsy	Clinically Significant	37	21	3	61
	Clinically Insignificant	24	30	5	59
	No cancer	7	25	30	62
	Totals:	68	76	38	182

Table 2. 6: Cancer detection using Harnden definition

Adapted, with permission, from [53]. Sensitivity analysis with definition of clinical significance as any cancer with Gleason grade 3+4 or maximum cancer core length of 3mm or greater. Each number in a box represents 1 patient. Since each man underwent both biopsy tests, they will have a classification for MRI-targeted biopsy and for transperineal template biopsy. The two tests agree where both detect clinically significant cancer (94 men), both detect clinically insignificant cancer (5 men) and both detect no cancer (30 men). They disagree with their classification in all other boxes. For example, where MRI-targeted biopsy detects clinically significant cancer in 121 men, 20 of these men were classified as having no cancer by template biopsy.

		Template Biopsy			
		Clinically Significant	Clinically Insignificant	No cancer	Totals:
MRI-Targeted Biopsy	Clinically Significant	94	7	20	121
	Clinically Insignificant	6	5	1	12
	No cancer	8	11	30	49
	Totals:	108	23	51	182

2.4 Discussion

The main finding of this study was that MRI-targeted biopsy detected a similar amount of clinically significant cancer as transperineal template prostate biopsy but with far fewer cores required. In addition, fewer men were diagnosed with clinically insignificant cancer. This outcome was consistent amongst a range of different definitions of significant cancer.

From the sampling density seen for the systematic biopsy of 0.88 biopsies per ml of tissue, the transperineal template sampling in this cohort was particularly

detailed. Thus, the ability of MRI-targeted biopsy to detect a similar amount of clinically significant cancer as such a detailed test like this is encouraging. Also encouraging was that this was achieved with visual registration, without the need for dedicated and often expensive software for MRI/US fusion registration [55]. There is uncertainty in the literature on whether using the dedicated MRI/US fusion software offers advantages over visual registration [56], and though this study does not compare the two, it does show good detection rates of significant cancer with visual registration. A visual registration MRI-targeted biopsy approach may be more generalizable to other centres which may not have access to MRI/US fusion equipment.

Perhaps an expectation that MRI-targeted biopsy detects more cancer than transperineal template prostate biopsy is optimistic, and this study confirmed that this was the case. Despite being very detailed, a transperineal template prostate biopsy does not detect all of the cancer in the prostate despite sampling throughout the prostate. This was demonstrated by the fact that MRI-targeted biopsy detected 17% of significant cancers not detected by transperineal prostate biopsy. This shows that the process of targeting a biopsy to an MRI-suspicious area can lead to sampling of disease that even a transperineal template biopsy would miss. This also highlights one of the challenges in prostate cancer diagnostic test evaluation. As we know there is no perfect reference standard, a comparison of two tests, as done here, is important as it allows the cancer detected by one test but not the other to be identified. These findings were also seen with studies published previously to this one, with Miyagawa et al showing that MRI-targeted biopsy detected 21% of cancers missed by systematic biopsy [57].

Given MRI-targeted biopsy missed some significant cancer that systematic biopsy detected, one good option to maximise the amount of clinically significant cancer detected would be to combine MRI-targeted and systematic biopsy. However, this approach would lose the advantage of avoiding the detection of clinically insignificant cancer which is a critical factor to consider. In this study, by avoiding the systematic biopsy, 8% of men could have avoided a diagnosis of clinically insignificant disease, the psychological morbidity of a diagnosis, the risk

of treatment in the absence of clinically significant disease and the risk of side effects from undergoing treatment. In addition, the costs of avoiding the need for active surveillance should be considered. Active surveillance has been projected to cost US$28,784 over 10 years for each patient [58]. Other studies published prior to this one showed similar findings, with Haffner showing that 13% of insignificant cancer diagnoses could be avoided [52].

In addition, one needs to consider the burden of intensive sampling regimens such as combined systematic and targeted regimes. Here we saw a low proportion of men experience side effects, though they were assessed retrospectively from review of the notes so it is likely that this is subject to reporting bias and that the incidence of side effects is higher than reported in the study. In prospectively evaluated studies in men with a similar biopsy approach and sampling density, 24% of men experienced urinary retention, 20% experienced erectile dysfunction and 9% experienced urinary tract infection [25]. This harm to patients could be mitigated by an MRI-targeted only approach which detected cancer in a far more efficient way, requiring in this study a median of only 5 cores per patient compared to 30 cores per patient for systematic biopsy. A more burdensome procedure takes up more theatre time, is more time-consuming for the pathologist and services typically struggle to cope with the volume of referrals coming through for suspected prostate cancer when they adopt such a diagnostic approach.

The subgroup analyses by prior biopsy status highlight previously seen trends[59]. The significant cancer detection rates in biopsy naïve men were one of the highest reported in the literature, validating the accuracy of the biopsies in the study [57, 60]. Men with prior negative biopsy also had a lower rate of clinically significant cancer than men with no prior biopsy. In men with prior negative biopsy, who do harbour a cancer missed on the first TRUS biopsy, these are commonly anterior or midline tumours, which can get picked up on the MRI. Thus, the performance of MRI-targeted biopsy compared to systematic biopsy in this group of patients has been demonstrated to be superior to TRUS biopsy [61]. In this study, MRI-targeted biopsy appeared to perform slightly better in the prior negative biopsy subgroup compared to the other subgroups, detecting

the same number of men with significant cancer as the transperineal template biopsy in this subgroup. In the other subgroups, the transperineal template biopsy detected slightly more men with significant cancer, though overall there were no statistically significant differences and the numbers in the subgroups are small so should be interpreted with caution.

This study has a number of strengths. Firstly, the test that MRI-targeted biopsy is typically compared to in the literature is TRUS biopsy but in this study, we were able to evaluate it compared to transperineal template prostate biopsy. Data comparing these two techniques is rarer as the availability of the transperineal biopsy technique is more limited. Using this comparison test provided us with an opportunity to evaluate MRI-targeted biopsy against a very detailed comparator, thus highlighting what significant cancer MRI-targeted biopsy would miss if a very detailed test was available to a centre.

Secondly, the systematic biopsy cores were taken from each of the 20 Barzell zones irrespective of the location of the MRI-targeted biopsy cores, which allowed a true table of comparison to be drawn up for the two strategies to be compared. In other studies, the operator performing systematic biopsy often avoids biopsy of the same region that was targeted and assume the targeted biopsy results from a region apply to both the targeted and systematic biopsy [62]. This study shows that this assumption is not always correct as MRI-targeted biopsy detected some cancer than systematic biopsy did not and vice-versa and thus offers some methodological advantages for diagnostic test evaluation. Thirdly, the outcomes were consistent across a range of different thresholds for clinically significant cancer which increases the consistency and reliability of the findings.

However, there are limitations to this study. Firstly, the inclusion criteria included men who underwent a pre-biopsy MRI, MRI-targeted biopsy and systematic biopsy. This means by definition all of these men had MRI lesions. Consideration of men who underwent MRI and had no suspicious lesions should be taken into account when considering a prostate cancer diagnostic pathway.

Second, the operator performing the MRI-targeted biopsy and the systematic biopsy was the same and was aware of the MRI-lesions when performing the systematic biopsy. It would be feasible that knowledge of where the MRI lesions were could have influenced the performance of the systematic biopsy. This could conceivably bias the performance of the systematic biopsy in either direction. This might mean for example, that an operator carrying out the systematic biopsy is more likely (consciously or sub-consciously) to target an MRI lesion thus the performance of the systematic biopsy may be better than if the operator was not aware of the MRI information. Alternatively, it could have influenced the operator (consciously or sub-consciously) to avoid biopsying the same area that was targeted previously and this may have led to a worse performance of the systematic biopsy than if the operator was not aware of the MRI findings. A way to overcome this limitation would be to have two operators and blind the operator taking the systematic biopsy to the MRI findings. In addition, one could randomise the order in which the MRI-targeted and systematic biopsies were taken.

Thirdly, the centre at which the study was carried out was an expert centre and thus the quality of the MRI, ability of the reporting radiologists and urologists taking the biopsies may not be generalizable to the average centre. Centres wanting to adopt an MRI-targeted only biopsy strategy should understand the operating characteristics of their own MRI pathway and ensure that it is comparable to the published literature first.

In conclusion, this study showed that transperineal visually registered MRI-targeted prostate biopsy detected a similar proportion of men with clinically significant cancer as a detailed transperineal template systematic prostate biopsy but with far fewer cores. In addition, a greater proportion of men avoided a diagnosis of clinically insignificant cancer with MRI-targeted biopsy.

2.5 Statement of contribution

My personal contribution to this work is as follows:

- Study design: I made final decisions on study design.

- Acquisition of data: I was one of 2 people collecting data for this project. I was the main data collector, collecting data in every patient.
- Statistical analysis: I performed the main statistical analysis.
- Analysis and interpretation of data: I was responsible for the analysis and interpretation of the data.

Other key contributions to this work:

- My supervisor Mark Emberton came up with the concept for the study.
- My supervisors Mark Emberton, Caroline Moore and Jan van der Meulen and in addition Hashim Ahmed gave input into the study design.
- Robert Dufour assisted with data collection in the early stages of the project, though I redesigned the project and collected new data for each patient.
- Susan Charman confirmed the accuracy of my statistics and helped with the statistical presentation of data
- Alex Freeman (pathologist), Clare Allen and Alex Kirkham (radiologists) assisted by providing their interpretation of the data for the publication, though none contributed directly to the writing of this thesis chapter

2.6 Related publication

Kasivisvanathan V, Dufour R, Moore CM, Ahmed HU, Abd-Alazeez M, Charman SC, Freeman A, Allen C, Kirkham A, van der Meulen J, Emberton M.

Transperineal magnetic resonance image targeted prostate biopsy versus transperineal template prostate biopsy in the detection of clinically significant prostate cancer.

J Urol. 2013;189(3):860-6.

Chapter 3 Establishing standards for reporting of studies of MRI-targeted biopsy

The findings from the work in this chapter have been published in *European Urology* [63] and have been included as an international reporting guideline by the Enhancing the QUAlity and Transparency Of health Research (EQUATOR) network [64].

3.1 Introduction

Systematic reviews have identified that studies of MRI-targeted biopsy varied considerably in how well they reported their findings, and in the definitions used to characterise the interventions used in the studies. A set of international standards established for reporting studies of diagnostic accuracy (STARD guidelines) were poorly adhered to in the MRI-targeted biopsy literature [65]. These guidelines set out clear standards in reporting the title, abstract, population studied, test methods, statistical methods, results, discussion and conclusion of diagnostic studies. This meant when attempting to synthesise the data in the literature on MRI-targeted biopsy in order to establish its role, it was difficult to pool data from different studies due to the uncertainty associated with the reporting.

A key requirement to establish whether MRI-targeted biopsy can be a replacement to systematic biopsy is a study that reports both techniques. Indeed, it was identified that a number of studies reported only MRI-targeted biopsies without a comparison to systematic biopsy. In studies that do report both techniques in the same study and where a man receives both tests in the same biopsy session, cancer detection was often not given separately for the MRI-targeted biopsies and the clinical significance of the cancer was often not defined [51]. What could be established from these studies was that 63-95% of men with raised PSA or abnormal digital rectal exam undergoing MRI had a visible MRI lesion identified, that 42-70% of men had a biopsy positive for cancer and that only 2.3% of men with a non-suspicious MRI would have significant prostate cancer missed if they did not have a biopsy [51].

Recognising that MRI-targeted biopsy represented a slightly different group of studies to typical diagnostic accuracy studies, it was clear that if we wanted to be able to synthesise data from different studies in a meta-analysis comparing MRI-targeted to systematic biopsy, that we would need to improve the reporting standards of studies of MRI-targeted biopsy of the prostate. Thus, we set out to establish reporting standards by which these studies should be reported. As part of this objective, it would be necessary to standardise terminology related to MRI-targeted biopsy in order to be consistent with definitions used across different studies. In the absence of high quality evidence, expert consensus methodology is the methodology typically chosen for the derivation of reporting standards [46, 65].

The reason these studies are typically different from typical studies of diagnostic accuracy is that in prostate cancer there is typically no good reference test. Whole mount prostatectomy specimens do allow a detailed assessment for the presence or absence of cancer. However only men who test positive on the index test (i.e. systematic or MRI-targeted biopsy), and who are likely to carry features of high risk disease, undergo radical prostatectomy. Secondly, not all men who test positive chose radical prostatectomy as their treatment option. Therefore, if radical prostatectomy was chosen as a reference standard, it would introduce selection bias and results would only be generalizable to those with high risk disease on biopsy undergoing radical prostatectomy. There would be no patients with a negative index or reference test result meaning test performance characteristics not be possible to derive. Therefore, in order to assess the value of MRI-targeted biopsy compared to systematic biopsy, one typically compares the diagnostic performance in studies where both tests are carried out.

3.2 Methods

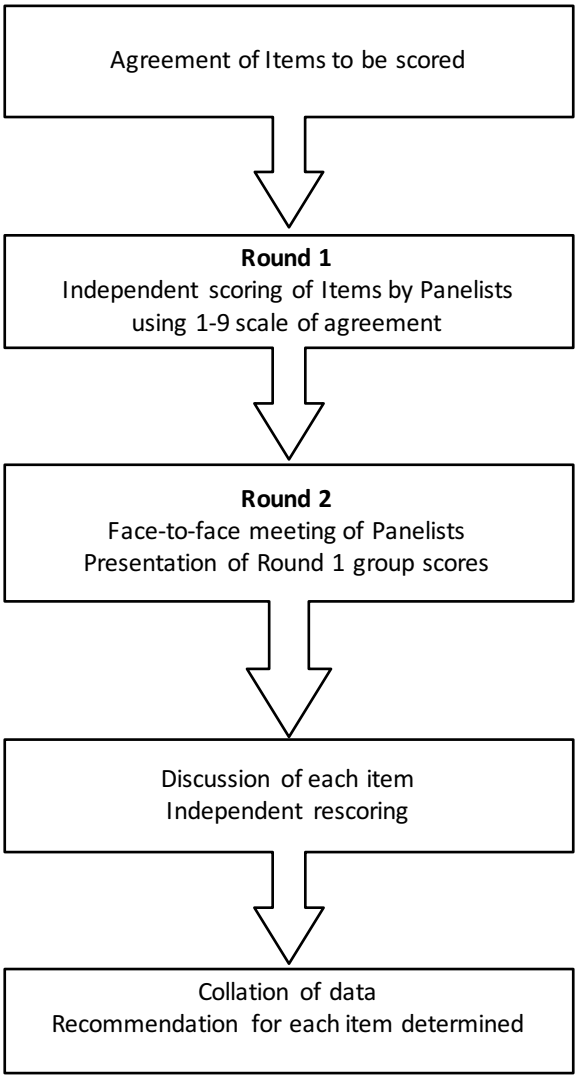
Following publication of a systematic review of MRI-targeted biopsy [51], a working group, the STAndards for Reporting studies of MRI-Targeted biopsy (START) consortium, was set up. Researchers and clinicians with expertise in MRI-targeted biopsy, as evidenced by published literature, were invited to participate (Table 3. 1).

Table 3. 1: Institutions and researchers comprising the START consortium

Institution	Researcher
CHU Lille, University Lille Nord de France	Philippe Pueche, Radiologist Arnauld Villers, Urologist
Erasmus Medical Centre, Rotterdam, Netherlands	Ivo Schoots, Radiologist
Kurashiki Central Hospital, Kurashiki, Japan	Yuji Watanabe, Radiologist
National Institute for Health, Bethesda, USA	Peter Pinto, Urologist Richard Simon, Methodologist Baris Turkbey, Radiologist
New York University Langone Medical Centre, USA	Jonathan Melamed, Histopathologist Andrew Rosenkrantz, Radiologist Samir Taneja, Urologist
Radboud University Medical Centre, Nijmegen, Netherlands	Jurgen Fütterer, Radiologist
Sunnybrook Hospital, Toronto, Canada	Laurence Klotz, Urologist
University of California, Los Angeles, USA	Daniel Margolis, Radiologist Leonard Marks, Urologist
University of Chicago, USA	Scott Eggener, Urologist Aytekin Oto, Radiologist
University College London, London, UK	Mark Emberton, Urologist Caroline Moore, Urologist Veeru Kasivisvanathan, Urologist Shonit Punwani, Radiologist
University of Southern California, Los Angeles, USA	Inderbir S Gill, Urologist Suzanne Palmer, Radiologist Osamu Ukimura, Urologist
University Hospital Heidelberg, Heidelberg, Germany	Boris Hadaschik, Urologist
Washington University School of Medicine, St Louis, USA	Robert Grubb, Urologist
London School of Hygiene and Tropical Medicine	Professor Jan van der Meulen, Epidemiologist

This was a multidisciplinary group including methodologists, radiologists, urologists and pathologists. Within this working group we ran a consensus meeting using RAND Corporation and University of California, Los Angeles (RAND/UCLA) appropriateness method consensus methodology [66]. This methodology was typically originally used in assessing the appropriateness of the use of healthcare resources but more recently has expanded to establishing requirements for reporting guidelines[46]. An overview of the RAND/UCLA consensus methodology is given in Figure 3. 1.

Figure 3. 1: Overview of the RAND/UCLA pathway

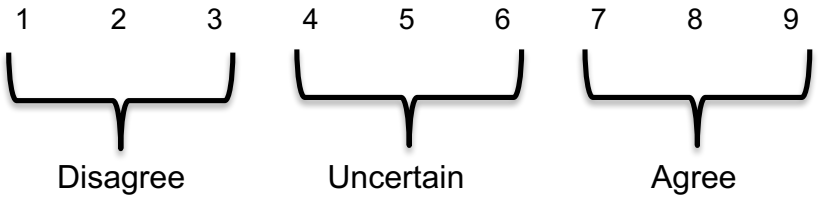


The first stage of this involved writing a list of statements for discussion pertaining to standards of reporting for MRI-targeted biopsy, which covered a full range of reporting domains in the subject, including the study title, methodology, population studied, conduct and reporting of the MRI, conduct of the biopsy,

results and discussion. The questions were generated by the authors from the lead institution. Following this, the questions were sent round to the wider group for their input and modifications. Two rounds followed this, the first carried out electronically and the second carried out in person.

In the first round, each statement was scored with agreement by a panel member by assigning the item a single score on a scale of 1-9. This is an ordinal scale where 1 was the least amount of agreement possible and 9 was the strongest agreement possible. A score of 1-3 meant that the panellist disagreed with the statement; a score of 4-6 meant that the panellist was uncertain about the statement; a score of 7-9 meant that the panellist agreed with the statement. Scoring was done independently without conferring.

Figure 3. 2: Range of scores possible for each item



The group median score for each item gave a summary measurement of how much the group agreed with the statement. However, for an item to be considered for inclusion in the final reporting guideline, it needed to be scored with consensus. The group median score ignores the measure of spread of answers in a group. If for example many panellists disagreed with a particular statement, some were uncertain but the majority agreed, the group median score might be within the agreement range (7-9) but the spread of answers may have been quite wide, meaning the item may not have been not scored in consensus. Each statement could either be scored with consensus, without consensus or as uncertain based on the spread of answers. The classical RAM criteria were used to derive thresholds for how many people were needed to score in the same range for it to be scored with consensus. For example, for an item being scored by 23 panellists, 16 were required to score the item in the same range for it to be scored with consensus.

The second round of the consensus meeting was carried out at a 2-day face to face meeting attended by the panellists at New York University Langone Medical Centre. This part of the meeting was chaired and mediated by a methodologist, with experience of chairing consensus meetings. As part of the consensus methodology, key definitions on terminology for MRI-targeted biopsy were established at the start of the meeting and items from the first round could be modified to increase clarity, removed if redundant or new items could be added if deemed important.

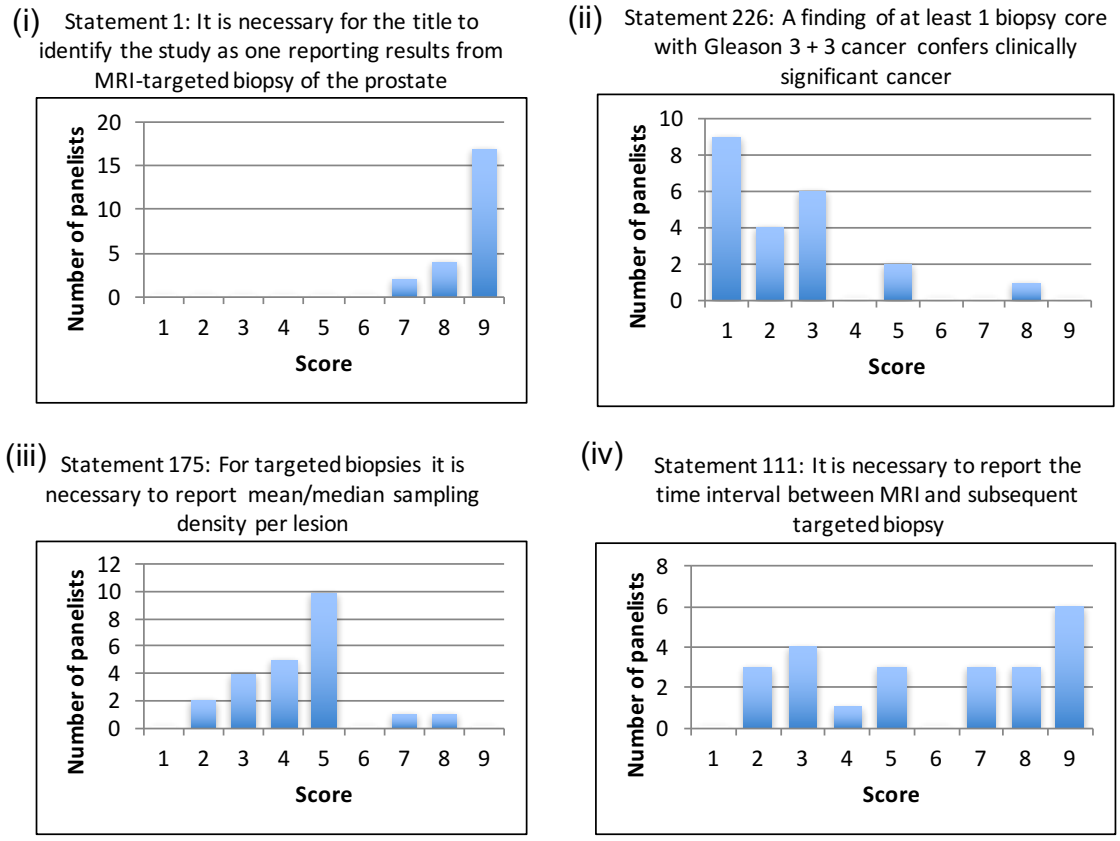
The graphical summaries of the group's level of agreement and degree of consensus for each item from the first round were presented to the group one after the other. Examples of this are given in Figure 3. 3. A discussion led by the chair then followed to identify areas where there was disagreement and lack of consensus. Different points of view surrounding a particular item were raised by the panellists after which they were then asked to independently and anonymously rescore that item for agreement according to the same 1-9 score, on paper copies of the questions.

Following the second round, scores for each item were collated and the group median score from this round was used to derive the level of agreement for each item, and as before, the classical criteria for consensus were used to assess the degree of consensus with which each item was scored. The items scored with the strongest consensus were included in the START checklist for recommended items to be included in reports of MRI-targeted biopsy of the prostate.

Ethical approval was not required for this study.

Figure 3. 3: Examples of graphical summaries of groups level of agreement and degree of consensus for 4 items

Reproduced, with permission, from [63]. (i) shows an example of a statement that scored with agreement and consensus. The group median score was 9 and no panelists scored outside the 7-9 range containing the median. (ii) shows an example that scored with disagreement and consensus. The group median score was 1 and only 3 panelists scored outside of the 1-3 range containing the median. (iii) shows an example scored with uncertainty. The group median score lies in the 4-6 uncertain range. (iv) also shows an example scored with uncertainty. Though the group median score of 7 lies in the 7-9 agreement range, as there are 11 panelists outside of this range, the item is given an uncertain recommendation.



3.3 Results

3.3.1 Agreed terminology for MRI-targeted biopsy

A group of important definitions pertaining to MRI-targeted biopsy were agreed upon and are specified in Table 3. 2

Table 3. 2: Agreed terminology for MRI-targeted biopsy

Reproduced with permission from [63].

Term	Description
MRI-targeted biopsy	Any biopsy technique where an MRI scan is used to determine the location of a suspicious target prior to biopsy.
Guidance during MRI-targeted biopsy	Method of assistance used by the operator in directing the biopsy needle at a target originally identified on MRI. Guidance is usually carried out using ultrasound or MRI.
Image registration.	Image registration is required to match the image of the target defined on MRI with the real-time image of the prostate during the biopsy procedure. This registration can be done with or without the use of software.
Visual registration	The target identified on MRI is registered to the real-time biopsy ultrasound image by the biopsy operator without the use of software. This has also been referred to as cognitive registration in the literature.
Software registration	The target identified on MRI is registered to a real-time biopsy ultrasound image by use of computer-based software which overlays the target onto the ultrasound image. This has also been referred to as MRI/TRUS fusion in the literature.
Direct in-bore biopsy	Biopsy technique carried out within the MRI scanner, where the target identified on MRI is biopsied using guidance from serial MRI-scans during the biopsy procedure. Commonly, a high quality diagnostic scan is performed to identify the target and the procedure is carried out in a lower strength open or interventional magnet.
Robot-assisted biopsy	Any biopsy where a robotic device is used to move the biopsy needle.

Of note, the key defining features of an MRI-targeted biopsy is that an MRI is performed prior to a biopsy, identifies a suspicious area and influences how the subsequent biopsy is taken. We deliberately differentiated this from a commonly used term in the literature, MRI-guided biopsy. MRI-guided biopsy had been used by some authors to refer to real time in-bore MRI-guided biopsy and by others to mean what we have defined as an MRI-targeted biopsy. For clarity, we avoided the use of the word MRI-guided biopsy altogether and chose to describe a biopsy carried out within an MRI scanner with MRI-compatible equipment as a “direct in-bore” MRI-targeted biopsy instead. We differentiated between two classical methods of relating the location of the suspicious area on MRI to the real-time ultrasound used during the procedure. In software registration or software-assisted registration, the MRI image with the suspicious lesion is superimposed onto the real-time ultrasound image during the biopsy procedure to help guide the operator to direct their biopsy needle into the location of the MRI lesion. In visual registration, the operator uses their own judgement to register the anatomical landmarks seen on the real-time ultrasound with the pre-biopsy MRI landmarks and lesion location. This means that during the biopsy procedure in visual registration, no software is used to assist the operator with the MRI lesion location. In the literature, cognitive registration is used synonymously with visual registration, but visual registration was preferred as the optimal descriptive term as “cognitive” implied falsely that when carrying our software-assisted registration, that there was less cognitive input from the operator.

3.3.2 Level of consensus after round 1 and round 2

For the consensus meeting scoring, there were 258 items scored in round one. After modification of items including removing some redundant items, at round two, there were 234 items to be scored (Table 3. 3). After round one, 44% (114/258) items were scored with consensus and after round two, 51% (120/234) items were scored with consensus.

Table 3. 3: Full list of items for scoring in round 2 and the level of agreement and consensus for each item

Reproduced with permission from [63].

Statement	Disagreement with consensus	Uncertain	Agreement with consensus
Section 1. Title of study report It is necessary to include the following information:			
1. Identification as a study reporting results from MRI-targeted biopsy of the prostate			X
2. The method of registration and guidance for MRI-targeted biopsy of the prostate carried out (e.g. visual or software registration, and US-guidance or MRI-guidance)			X
3. The endpoint e.g. detection of clinically significant prostate cancer or detection of prostate cancer.		X	
4. The population studied e.g. biopsy naïve, negative initial biopsy, active surveillance.		X	
Section 2: Introduction It is necessary to report the following:			
5. A clear statement of the research question or study aim e.g. the comparison of the detection of clinically significant prostate cancer using a standard versus targeted biopsy approach.			X
Section 3: Study Methodology It is necessary to report the following:			
6. The setting (public hospital, academic centre, multi-centre studies).			X
7. The location of the study (city/country).		X	
8. The dates between which the study recruited and followed up patients.			X
9. Whether data collection was prospective or retrospective			X
10. The study design (cohort; randomised).			X

11. Whether any of the reported patients have been included in previously reported cohorts.			X
12. Whether recruitment was based on PSA values alone, or results from other tests such as MRI, TRUS or biopsy			X
Section 4: Study Population It is necessary to report the following:			
13. Number of men who have never had a previous prostate biopsy			X
14. Number of men who have had a previous prostate biopsy negative for cancer			X
15. Number of men who have had a previous prostate biopsy positive for cancer			X
16. Whether previous biopsies were performed within or outside of the study centre.		X	
17. The age range of study participants.			X
18. The PSA prior to biopsy (Mean/median and range).			X
19. Time between PSA and biopsy. (Mean/median and range).		X	
20. Number of men taking drugs which would affect the hormonal environment in the prostate (e.g. 5 alpha reductase inhibitors, anti-androgens, luteinising hormone releasing hormone (LHRH) analogues or antagonists).		X	
21. Number of men who have had previous treatment for prostate cancer.			X
22. Number of men who have had previous surgical or minimally invasive treatment for symptomatic prostate enlargement (e.g. transurethral resection of the prostate (TURP), laser treatment).		X	
23. Number of men excluded from study population due to inability to have MRI (e.g. pacemaker / claustrophobia / renal impairment).		X	
24. Number of men excluded from study population due to inability to have biopsy (e.g. comorbidites)		X	
25. Number of men who declined biopsy after MRI.			X
26. A flow chart of the numbers of men suitable to be considered for the study, those who were offered and accepted the study, those who were then excluded and those who completed the study.			X
27. The precise indications for prostate biopsy e.g. PSA range, PSA velocity, digital rectal examination findings			X
28. The number of men with a suspicious lesion on transrectal ultrasound (TRUS).		X	

29. The inclusion and exclusion criteria for chosen study centers and clinicians (e.g. minimum number of years of experience).		X	
30. Prostate volume (mean/median and range)			X
For men with previous prostate biopsies it is necessary to report the following:			
31. The biopsy route (transperineal/transrectal /transgluteal).		X	
32. The locations of cores from previous biopsies (i.e. the standard biopsy scheme)		X	
33. The time interval between previous biopsy and study MRI			X
34. The number of men with high-grade prostatic intraepithelial neoplasia (HGPIN).		X	
For men with previous negative prostate biopsies it is necessary to report the following:			
35. Mean or median number of sets of previous negative biopsies per man.			X
36. Mean or median number of biopsy cores per set		X	
37. Mean or median number of biopsy cores per man		X	
		X	
For men with previous positive prostate biopsies it is necessary to report the following:			
38. Mean or median number of sets of previous positive biopsies per man (e.g. men on active surveillance).		X	
39. Mean or median number of biopsy cores per set.		X	
40. Mean or median number of biopsy cores per man		X	
41. Mean or median number of biopsy cores positive for cancer per man		X	
42. The number of men with clinically significant cancer (along with a definition of the threshold used for clinical significance).			X
43. The number of men with each Gleason score category (e.g. 3+3, 3+4, 4+3, 4+4 etc).			X
44. The mean or median maximum cancer core length per man (including the intervening areas of benign glands)		X	
45. The mean or median maximum cancer core length per man not counting the intervening areas of benign glands (according to International Society of Urological Pathology (ISUP) criteria).		X	
46. The mean or median total percentage of biopsy material with cancer involvement per man.		X	

47. The mean or median maximum cancer core length as percentage of total cancer core length per man		X	
Section 5: Conduct of the MRI It is necessary to report the following:			
48. The manufacturer, make and model of the MR machine.			X
49. The field strength of the magnet.			X
50. The specific coils used (pelvic, endorectal).			X
51. A brief description of the sequences.			X
52. T2 – which planes acquired			X
53. DCE – temporal resolution			X
54. DCE- model used for post processing			X
55. DWI – b values used			X
56. DWI – which image sets analysed (high b value image, ADC map, both)			X
57. DWI – qualitative or quantitative analysis			X
58. The scan time per sequence.			X
59. The total scan time per patient.		X	
60. Use of an anti-peristalsis agent.		X	
61. Use of an enema prior to the MRI.		X	
62. Whether patient instructed to be 'nil by mouth' prior to the MRI.		X	
63. Whether the patient was instructed to abstain from sexual activity prior to the MRI.		X	
64. Slice thickness			X
65. True acquisition resolution based on the field of view and reconstruction matrix			X
Section 6: Reporting of the MRI It is necessary to report the following:			
66. The number of radiologists reporting scans at the study centre.		X	
67. The number of years experience of each radiologist in prostate MRI reporting.			X
68. Whether each scan is reported by more than one radiologist		X	
69. Where there is more than one radiologist reporting each scan, whether their reports are done separately, or in consensus.			X

70. Whether the MRI report is aimed at reporting any suspicious lesion, or only clinically significant prostate cancer (irrespective of the definition used).			X
71. The reporting method used, including the use of any scoring system for suspicion of prostate cancer, whether a prose report or diagrammatic report is used and whether embedded MRI images are used).			X
72. Whether any computer aided diagnosis (CAD) software was used for MRI interpretation.			X
73. The individual results of each of the MRI sequences (T1, T2, DCE, diffusion, MRS)		X	
74. The visual reporting scheme, if one is used (e.g. diagrams, MR snapshots within the report).			X
75. Whether a previously published reporting system is used e.g. PI-RADS[47]			X
76. The number of segments/sectors that are reported individually.		X	
77. The division of the prostate into different regions for reporting, in diagrammatic form.		X	
78. The threshold score used to determine need for biopsy (e.g. 3 and above in a 1-5 scale)			X
79. An overall score of likelihood of cancer for the whole prostate, based on analysis of all the available sequences.			X
80. An overall score of likelihood of clinically significant cancer for the whole prostate, based on analysis of all the available sequences.		X	
81. A score for each sequence (i.e. for T1, T2, DCE, diffusion, MRS).		X	
82. The sequence which most easily identifies the lesion should be identified.		X	
83. The criteria giving rise to each score for each sequence should be reported in detail.		X	
84. The criteria giving rise to each score for each sequence should be referenced where a previously published system is used e.g. PI-RADS[47]		X	
It is necessary to report whether the following patient information was made available to the radiologist reporting the scans:			
85. Whether or not the radiologist was blinded to clinical information			X
Section 7: Conduct of the biopsy It is necessary to report the following:			
86. The method of registration and guidance of MRI-targeted biopsy (e.g. visual or software registration and US-guidance or MRI guidance).			X
87. The person performing the biopsy (e.g. radiologist, urologist, technologist).			X
88. The approach used for access to the prostate (transrectal/transperineal/transgluteal).			X

89. An estimate of the time taken for each biopsy procedure		X	
90. The mean or median time taken for each biopsy procedure		X	
91. The number of years experience of the operator(s) in taking targeted biopsies using TRUS guidance.		X	
92. The number of years experience of the operator(s) in taking MRI-guided biopsies (in bore biopsies).		X	
93. The number of years experience of the operator(s) in taking prostate biopsies		X	
94. Whether cores are potted separately for targeted and standard techniques.			X
95. Whether cores from different standard biopsy locations are potted separately.			X
96. The time interval between MRI and subsequent biopsy (mean/median and range)		X	
It is necessary to report the following side effects and preventative measures related to the biopsy			
97. Adverse events from performing the biopsies			X
98. The use of a pre-biopsy enema		X	
99. The use of pre biopsy antibiotics		X	
100. The use of post biopsy antibiotics		X	
101. The use of an alpha-blocker to reduce urinary retention.		X	
102. The use of local anaesthetic (peri-prostatic or intra rectal).			X
103. The use of sedation.			X
104. The use of general anaesthetic.			X
For those studies where standard cores are taken, it is necessary to report the following:			
105. Whether standard cores are taken in all men.			X
106. The intended number of standard cores per prostate			X
107. The intended sampling density of standard cores per prostate (cores/ml).		X	
108. Whether the standard cores are taken by the same operator as the targeted cores.		X	
109. Whether the operator taking the standard cores is aware of or blinded to the MRI results.			X
110. In patients undergoing both targeted and standard biopsies, whether targeted biopsies or standard biopsies are taken first.			X
111. In patients undergoing both targeted and standard cores biopsies, whether the same area of the prostate is biopsied again if it is has already been biopsied by the first biopsy technique)			X

112. Whether additional cores are taken in men who have no lesion on MRI to target (i.e. to balance the increased the number of cores in men who have targeted cores in addition to standard standard cores).			X
For targeted biopsies, it is necessary to report the following:			
113. The intended number of biopsy cores per targeted lesion			X
114. The intended sampling density per targeted lesion (cores/ml)		X	
115. The criteria for choosing a lesion to be biopsied			X
116. Whether additional targeted biopsies from suspicious areas on TRUS, but not noted as suspicious on MRI, were taken.			X
For studies involving visual registration it is necessary to report the following:			
117. Whether the biopsy operator had direct access to the MRI images			X
118. Which MRI sequences were reviewed by the person performing the biopsy.		X	
119. Whether the biopsy operator views a diagrammatic report.		X	
120. Whether the biopsy operator reads a prose report		X	
121. Whether the biopsy operator is told distances of the target from critical structures		X	
122. Whether the biopsy operator identified any US-suspicious lesion (or US-identical anatomy) corresponding with the MR-suspicious lesion.		X	
123. In how many patients the biopsy operator identified a suspicious lesion on ultrasound which correlated with the MR suspicious lesion.		X	
124. Which TRUS probe was used (single plane, bi-plane, or 3D-probe)		X	
125. The operator's confidence or satisfaction of the precision of the sampling (e.g. (a)sure, (b)moderate, or (c)uncertain)		X	
For studies involving software registration it is necessary to report the following:			
126. The use of rigid or non-rigid registration			X
127. The time taken for the registration process.		X	
128. The software name and version.			X
129. Whether any re-registration was required based on any unreliable image-registration (by operator's decision).		X	

130. Whether the biopsy operator identified any US-suspicious lesion (or US-identical anatomy) corresponding with MR-suspicious lesion		X	
131. Which TRUS probe was used (single plane, bi-plane, or 3D-probe)			X
132. Which sequence of MRI is used for the image registration.			X
133. Whether the software confirmed that the targeted biopsy adequately sampled from the lesion (e.g. (a) hit the center, or (b) hit the periphery of the lesion)		X	
Section 10: MRI results It is necessary to report the following:			
134. Number of men undergoing MRI who had at least one suspicious lesion identified according to the study's pre-defined threshold of suspicion			X
135. Number of men who had an MRI with a suspicious lesion that went on to targeted biopsy			X
136. Number of lesions per patient identified by MRI (mean/median and range)			X
137. Total lesion volume per patient (mean/median and range) (e.g. if a patient has 2 lesions, the total volume for that patient would be the sum of the volume of both lesions)		X	
138. Lesion volume for the largest lesion only per patient (mean/median and range)		X	
139. Longest dimension of lesion(s) per patient (mean/median and range) (e.g. if a patient has 2 lesions, the longest dimension for that patient would be the sum of longest dimension of both lesions)		X	
140. Longest dimension for largest lesion only per patient (mean/median and range)		X	
Section 11: Biopsy results It is necessary to report the following:			
141. The mean/median number of lesions per patient from which at least 1 targeted core was taken			X
142. The total number of lesions in the population from which at least 1 targeted core was taken		X	
143. The total number of cores taken in the study population.		X	
144. Total number of cores positive for cancer in the study population.		X	
145. The proportion of cores positive for cancer (all positive cores/all cores taken) in the study population.		X	
146. Separate reporting of standard and targeted cores.			X

147. Reporting according to location or zone of origin using a diagram		X	
148. Location or zone of origin using a standardised reporting scheme e.g. peripheral cores, anterior cores etc.			X
For targeted biopsies it is necessary to report the following:			
149. The mean/median number of cores per prostate			X
150. The mean/median number of cores per lesion			X
151. The total number of cores taken in the population		X	
152. Total number of cores positive for cancer in the population		X	
153. The proportion of cores positive for cancer in the population			X
154. Mean/median sampling density per prostate (cores/ml of prostate)		X	
155. Mean/median sampling density per lesion (cores/ml)		X	
For standard biopsies it is necessary to report the following:			
156. The mean/median number of cores per prostate			X
157. The total number of cores taken in the population		X	
158. Total number of cores in population positive for cancer		X	
159. The proportion of the cores positive for cancer in the population			X
160. Mean/median sampling density per prostate (cores/ml of prostate)		X	
For men with a positive biopsy it is necessary to report the following histological features:			
161. The number of men in each Gleason score category (3+3, 3+4, 4+3, 4+4, 4+5 etc) using targeted cores alone.			X
162. The mean/median maximum continuous cancer core length per patient using targeted cores alone.			X
163. The mean/median total cancer core length per patient using targeted cores alone.		X	
164. The mean/median percentage cancer core length per patient using targeted cores alone		X	
165. The number of men in each Gleason score category (3+3, 3+4, 4+3, 4+4, 4+5 etc) using standard cores alone.			X
166. The mean/median maximum continuous cancer core length per patient using standard cores alone.			X

167. The mean/median total cancer core length per patient using standard cores.		X	
168. The mean/median percentage cancer core length per patient using standard cores alone		X	
For men with a positive biopsy who undergo both standard and targeted biopsies, it is necessary to report the following histological features:			
169. The number of men in each Gleason score category (3+3, 3+4, 4+3, 4+4, 4+5 etc) combining targeted and standard cores.			X
170. The mean/median maximum cancer core length per patient combining targeted and standard cores		X	
171. The mean/median total cancer core length per patient combining targeted and standard cores.		X	
172. The mean/median percentage cancer core length per patient combining targeted and standard cores.		X	
Section 12: Presentation of prostate cancer detection It is necessary for prostate cancer detection to be reported:			
173. Combined for patients regardless of prior biopsy status		X	
174. Separately for patients who have never had a biopsy, had a prior negative biopsy or had a prior positive biopsy			X
175. Combined for patients regardless of prior biopsy status but presented together with breakdown by prior biopsy status		X	
In studies where each patient has both standard and targeted biopsies it is necessary for cancer detection to be reported:			
176. As the total number of men with cancer detected by both standard and targeted biopsies (i.e. their individual contributions cannot be derived)		X	
177. Separately for targeted and standard biopsies			X
178. As the number of men with cancer detected by standard biopsies alone, targeted biopsies alone and detection when the results from both are combined			X
179. In a cross tabulation of the number of men with cancer detected by targeted biopsies against the number of men with cancer detected by standard biopsies			X
180. By specifying the number of men with clinically significant cancer detected by targeted			X

biopsies			
181. By specifying the number of men with clinically significant cancer detected by standard biopsies			X
182. By specifying the number of men with clinically significant cancer detected by either targeted or standard biopsies.			X
183. By specifying the number of men with clinically insignificant cancer identified by targeted biopsies			X
184. By specifying the number of men with clinically insignificant cancer identified by standard biopsies			X
185. By specifying the number of men with clinically insignificant cancer identified by either targeted or standard biopsies.			X
186. By specifying the number of men positive at standard biopsy and negative at targeted biopsy.			X
187. By specifying the number of men negative at standard biopsy and positive at targeted biopsy			X
188. By specifying the number of sextants with any cancer by either targeted or standard biopsies.		X	
189. By specifying the number of sextants with clinically significant cancer by either targeted or standard biopsies		X	
190. As the number of men with positive cores drawn on a prostate map [52]		X	
191. As the number of men with positive cores drawn on a sector diagram of the prostate e.g. sextant/12 sector/20 sector		X	
192. By comparing detection of cancer by standard and targeted cores on a sector level e.g. anterior prostate, posterior prostate		X	
193. By comparing the targeted cores with the highest Gleason score or longest cancer core length for each patient to the standard cores with the highest Gleason score or longest cancer length from the same patient			X
Section 13: Defining clinically significant disease: Clinical significance of prostate cancer should be reported:			
194. With sub-classification into clinically significant and clinically insignificant cancer			X

195. With more than 1 threshold for clinical significance explored		X	
The following parameters should be reported and included in the definition of clinically significant prostate cancer when using MRI-targeted biopsy:			
196. Gleason grading			X
197. Maximum continuous cancer core length not counting the intervening areas of benign glands (according to the method recommended by the International Society of Urological Pathology).			X
198. Total cancer core length		X	
199. PSA		X	
200. PSA Density		X	
201. MRI lesion volume		X	
202. Treatment choice		X	
203. Risk stratification using previously published criteria		X	
On a per patient level the following finding in at least one biopsy core from MRI-targeted biopsy confers clinically significant prostate cancer:			
204. Gleason 3+3	X		
205. Gleason 7		X	
206. Gleason 3+4		X	
207. Gleason 4+3			X
208. Gleason ≥ 8			X
209. MCCL > 2mm and/or Gleason ≥ 3+4 (Goto criteria)		X	
210. MCCL ≥ 3mm and/or Gleason ≥ 3+4 (Harnden criteria)		X	
211. MCCL ≥ 4mm and/or Gleason ≥3+4 (UCL definition 2)		X	
212. MCCL ≥ 5mm and/or Gleason ≥ 3+4 (Haffner criteria)		X	
213. MCCL ≥ 6mm and/or Gleason ≥4+3 (UCL definition 1)			X
214. The criteria used for the definition of clinically significant cancer should be stated			X
On a per patient level the following criteria confer clinically significant prostate cancer:			
215. D'Amico intermediate risk (T2b or Gleason score 7 or PSA >10 and <20ng/ml)			X

216. D'Amico high risk (T2c, Gleason score ≥ 8 or PSA > 20ng/ml)			X
217. Stage T1a/N0/M0	X		
218. Stage T1b/N0/M0		X	
219. Stage T1c/N0/M0		X	
220. Stage T2a/N0/M0		X	
221. Stage T2b/N0/M0		X	
222. Stage T3a/N0/M0			X
223. Stage T3b/N0/M0			X
224. Any N1			X
225. Any M1			X
Section 14. Statistical analysis Where possible ,it is necessary to report the following:			
226. Methods used to calculate or compare measures of diagnostic accuracy and the statistical methods used to quantify uncertainty			X
227. For prospective studies the assumptions involving the sample size should be stated			X
228. All numerators and denominators should be reported in either the text or table for all percentages.			X
229. Estimates of the variability of diagnostic accuracy between subgroups of men, readers, or centres		X	
230. Sensitivity, specificity, accuracy, and positive and negative predictive values.		X	
Section 15: Discussion It is necessary for the following to be discussed:			
231. The clinical applicability of the study findings.			X
232. The comparison of the proportion of targeted cores positive for clinically significant cancer to the proportion of standard cores positive for cancer.			X
233. The sampling efficiency of targeted biopsy compared to standard biopsy (e.g. mean number of cores per cancer diagnosis).			X
234. The comparison of the number of men diagnosed with cancer by targeted biopsy compared to standard biopsy			X

The key recommendations scored with consensus were divided up into key domains related to the writing of a paper reporting MRI-targeted biopsy:

3.3.3 Recommendations for reporting the title and introduction

The study should identify itself as one that reports results from MRI-targeted biopsy of the prostate with a clear statement of the study aim.

3.3.4 Recommendations for reporting the study methodology

The study design should be stated, specifying whether it was prospective, retrospective, a cohort study or a randomized study. The dates of recruitment of men included in the study should be specified, detailing if any had been included in previously published cohorts. The eligibility criteria for men included in the study should be specified, specifically if recruitment was related to PSA values or other test results.

3.3.5 Recommendations for reporting the study population

The prior biopsy status of the men included in the study should be specified, detailing the number of men without prior biopsy, with prior negative biopsy and with prior positive biopsy. If any of the men had had treatment to the prostate, this should be specified and explained in more detail. Key summary measures to report for the patient population would be the pre-biopsy PSA, prostate volume and age. A flow chart of the study flow should be given, detailing any exclusion reasons for men who do not complete the study.

3.3.6 Recommendations for reporting the MRI conduct in the study

As a minimum, the field strength of the MRI magnet and coils used (e.g. body surface coils, endorectal coils) should be specified. There should be a brief description of the slice thickness and true acquisition resolution for each sequence. For T2-weighted imaging, the planes acquired should be specified; for dynamic contrast enhanced imaging, the temporal resolution and model used for

post processing should be specified; for diffusion weighted imaging, the b-values used and the image sets used for analysis should be specified.

The scoring system used to indicate likelihood of significant cancer (e.g. Likert or PI-RADs) should be specified, indicating how the radiologist portrayed the information to the biopsy operator (e.g. diagrammatic report, mark on actual images, prose report) and whether the radiologist was blinded to the clinical information. The experience of the radiologist should also be specified.

3.3.7 Recommendations on reporting of the conduct of the biopsy

The order in which the MRI-targeted and systematic biopsy cores were taken should be specified, detailing which was taken first, the access route and whether the cores were stored separately. The registration method and real-time guidance during the procedure should be specified. If visual registration was performed, it should be detailed whether the MRI images were available for the operator to view or whether it was simply a report. For software registration, the details of the software, what sequence on MRI was used for registration and whether registration was rigid or non-rigid should also be specified.

3.3.8 Recommendations on reporting of the results of the study

The number of men who had MRI-targeted biopsy and the number of men with a suspicious MRI should be reported. The number of cores taken per prostate should be given for both MRI-targeted and systematic biopsy. The proportion of cores positive for cancer for the MRI-targeted biopsies and the systematic biopsy cores should be given. The number of men with clinically significant and insignificant cancer detected by targeted cores and systematic cores should be given separately. The definition of clinical significance used in the study should be specified and the study results should also be presented by Gleason grade categories. A table of agreement with the number of men with clinically significant, insignificant and no cancer detected by MRI-targeted biopsy compared to systematic biopsy should be given (See Table 3. 4 for an example).

Table 3. 4: Table of agreement for histopathological results of MRI-targeted and systematic biopsies

Adapted, with permission, from [63].

		Systematic biopsies		
		No cancer	Clinically insignificant disease	Clinically significant disease
No MRI target				
MRI-targeted biopsies	No cancer			
	Clinically insignificant disease			
	Clinically significant disease			

3.3.9 Recommendations on writing the discussion of the study

There should be a discussion on the implications of the cancer detection and proportion cores positive for cancer by MRI-targeted biopsy and systematic biopsy and comparisons between the two should be made.

3.3.10 Areas of uncertainty

Table 3. 5 describes controversial areas which were scored as being uncertain following a group discussion and rescoring. Of note, for the MRI reporting, there was uncertainty as to whether the detailed criteria giving rise to each score for each sequence needed to be given and whether when reporting the MRI, it was necessary to divide up the prostate into separate regions on a diagrammatic report. It was also not certain whether the average MRI lesion volume needed to be reported. With regards to reporting the histopathological results of MRI-targeted biopsy, there was uncertainty as to whether the average total cancer core length or the average percentage of core length involved with cancer needed to be reported, as either would be influenced by the sampling strategy and number of cores taken, not just tumour burden. There was also uncertainty as to whether cancer detection should be presented by different definitions of clinical significance. The discussion on clinical significance highlighted that we

could not all agree on a universal histopathological definition of clinical significance for MRI-targeted biopsy.

Table 3. 5: Notable items scored with uncertainty

Reproduced, with permission, from [63].

There is uncertainty in whether the following should be reported:
Reporting of the MRI
The detailed criteria giving rise to each score for each sequence
The individual results of each of the MRI sequences (T2WI, DCE, DWI, MRS)
Identification of the sequence which most easily identifies the lesion.
The division of the prostate into different regions for reporting, in diagrammatic form.
An overall score of likelihood of clinically significant cancer for the whole prostate, based on analysis of all the available sequences.
MRI Results
Mean/median MRI lesion volume per patient
Mean/median sum of longest dimensions of lesions per patient
Biopsy results
The mean/median total cancer core length per patient
The mean/median percentage of core length involved with prostate cancer per patient
Cancer detection classified by the number of sextants with cancer
Cancer detection classified according to location or zone of origin
Cancer detection depicted by specifying location of positive cores on a diagrammatic representation of the prostate
Cancer detection using more than 1 threshold for clinical significance
DCE – dynamic contrast enhanced imaging, DWI – diffusion weighted imaging, MRS – magnetic resonance spectroscopy, T2WI – T2-weighted imaging

3.3.11 START checklist

The summary of main items that should be included in a report of MRI-targeted biopsy are given in Table 3. 6. These are the items that were scored with the strongest consensus.

Table 3. 6: START Checklist of recommended items to report for MRI-targeted biopsies

Reproduced, with permission, from [63].

START Checklist **In studies of MRI-targeted biopsies, it is recommended to report the following:**		Page no.
Title and Introduction		
1	Identification as a study reporting results from MRI-targeted biopsy of the prostate with a clear statement of the study aim	
Study Methodology		
2	The study design (e.g. prospective or retrospective, cohort or randomized)	
3	The dates of recruitment, including whether any men have been included in previously published cohorts.	
4	Whether recruitment was based on PSA values alone or results from other tests such as MRI, TRUS or biopsy	
Study Population		
5	The biopsy and treatment status of the population, specifying: a. Number of men without prior biopsy b. Number of men with prior biopsy negative for cancer c. Number of men with prior biopsy positive for cancer and the number of men in each Gleason score category (e.g. 3+3, 3+4, 4+3, 4+4) d. Number of men with previous treatment to the prostate	
6	Summary measures (range & mean or median) for age, prostate volume and pre-biopsy PSA.	
7	A flow chart of the number of men who were suitable for study inclusion, those who were then excluded (with reasons specified), and those who completed the study	
Conduct and reporting of the MRI		
8.	The field strength of the magnet, specific coils used (e.g. pelvic, endorectal) and a brief description of the sequences to include: a. Slice thickness and true acquisition resolution based on the field of view and reconstruction matrix for T2-weighted imaging, DWI and DCE b. For T2-weighted imaging, which planes were acquired c. For DCE, the temporal resolution and the model used for post processing d. For DWI, the b-values used, which image sets were analysed (e.g. high b-value image, ADC map or both) and whether qualitative or quantitative analysis was carried out	

9	The reporting method used, including the use of any scoring system for suspicion of prostate cancer, whether a prose or diagrammatic report was used and whether the radiologist was blinded to the clinical information.	
10	The experience of the reporting radiologist (e.g. number of years).	
Conduct of the biopsy		
11	Whether targeted cores or standard cores were taken first, whether they were potted separately and the approach used for each technique (e.g. transrectal, transperineal)	
12	The method of registration and guidance used for MRI-targeted biopsy including: a. The type of registration used (e.g. visual or software registration) b. For visual registration, whether the biopsy operator had direct access to the MRI images, or used a prose or diagrammatic report. c. For software registration, the software name and version, the MRI-sequence used for registration and whether registration was rigid or non-rigid d. The guidance used during the biopsy procedure (e.g. ultrasound or MRI)	
13	Whether the person taking the standard cores was aware of the location of the lesion on MRI.	
Results		
14	The number of men who had an MRI with a suspicious lesion and the number who had an MRI-targeted biopsy	
15	A summary measure (mean or median) of the number of targeted cores taken per prostate or per lesion and of the number of standard cores taken per prostate	
16	The number of men in each Gleason score category (e.g. 3+3, 3+4, 4+3, 4+4) from targeted cores alone and standard cores alone	
17	The number of men with clinically significant and clinically insignificant cancer detected by standard cores alone and targeted cores alone, with the criteria used for the definition of clinically significance	
18	A cross-tabulation of the number of men with clinically significant and clinically insignificant cancer detected by targeted biopsies against the number detected by standard biopsies	
19	The proportion of cores positive for clinically significant cancer in targeted cores alone and standard cores alone, and the mean number of cores taken per diagnosis of clinically significant cancer for each technique.	
Discussion		
20	A comparison between targeted and standard biopsy techniques for: a. Proportion of cores positive for clinically significant cancer b. Sampling efficiency (e.g. mean number of cores taken per diagnosis of clinically significant cancer) c. Number of men diagnosed with clinically significant and clinically insignificant cancer	
DCE – dynamic contrast enhanced imaging, DWI – diffusion weighted imaging, TRUS – transrectal ultrasound		

3.3.12 Case report Form

For investigators to report their study by the recommended guidelines it is important to know what data to collect on an individual patient level. Thus, Table 3. 7 shows an example case report which an investigator may wish to follow or adapt for their study in order for their final report to be START compliant.

Table 3. 7: Case report form consistent with reporting by START guidelines

Adapted, with permission, from [63].

Patient Details	
Study number	
Date of birth	
Patient History	
Prior biopsy status (none, positive, negative)	
Prior biopsy details: • Number of previous biopsy sessions • Date of most recent biopsy session • Type of biopsy (e.g. standard transrectal) • Any set positive for clinically significant cancer • Definition of clinical significance used • Gleason score category (3+3, 3+4, 4+3 etc)	
Prostate treatment to date (functional or cancer related)	
Prostate volume (MRI or US calculated)	
PSA prior to study biopsy	
Study MRI	
Date of MRI	
MRI description (e.g. coil strength, sequences used)	
Reason for MRI (eg raised PSA, abnormal DRE, biopsy result)	
Name and years experience of radiologist reporting MRI	
Reporting method (prose, drawing, MRI snapshots)	
Was the radiologist blind to clinical information?	
Number of lesions (targets) identified on MRI	
Score of likelihood of cancer for each lesion	
Study biopsy procedures	
Type of biopsy procedure(s) performed (e.g. 10-12 core standard transrectal prostate biopsies, MRI-targeted transrectal biopsies)	
Reason for biopsy (e.g. raised PSA, abnormal DRE, MRI result)	
Date of biopsy procedure	
What order were the biopsy procedures carried out in?	
Standard cores biopsy operator aware of the location of MRI targets?	
Name of operator performing each biopsy procedure	
Registration method(s) (e.g. visual or software, inc. name & version, sequence used for registration, rigid or non-rigid registration)	

Visual registration: did the biopsy operator use MRI images, prose or diagrammatic report?	
Guidance during each biopsy procedure (ultrasound or MRI)	
Biopsy related adverse events (date & details)	
Targeted biopsy procedure	
Number of targets biopsied	
Number of cores from each target	
Total number of targeted cores	
Non-targeted biopsy procedure (if applicable)	
Total number of standard cores	
Histological results **Targeted Biopsy**	
Number of cores positive for any cancer (in total and specified for each target)	
For each target positive for cancer: • Gleason score • Maximum cancer core length	
Targeted cores positive for clinically significant cancer?	
Targeted cores positive for clinically insignificant cancer?	
Non-targeted biopsy procedure	
Number of cores positive for cancer	
If positive for cancer: • Gleason score • Maximum cancer core length	
Standard cores positive for clinically significant cancer?	
Standard cores positive for clinically insignificant cancer?	

3.4 Discussion

The main outcomes of this study were to identify a list of key items in the START checklist which describe what should be reported in studies of MRI-targeted biopsy. The purpose of these items is to improve the reporting standards of these studies so that the role of MRI-targeted biopsy in relation to systematic biopsy can be more robustly evaluated. It is anticipated that studies reported according to the START guidelines will allow for synthesis of data and meta-analysis of these studies in the future. It is also anticipated that investigators should use the checklist when designing their MRI-targeted biopsy studies and writing up their study results. We would recommend that the START checklist is included in an appendix of a study, with the page numbers that each item is reported specified.

The identification of the study as one of MRI-targeted biopsy in the title is important as is the standardisation of some terminology during the meeting. This will be important during the title and abstract screening phase of a systematic review of this topic, allowing screeners to appropriately include these studies and making them less likely to exclude a study in error. Specification of the study design is key, with prospective studies perhaps being less prone to some biases than retrospective studies. The choice of a paired cohort design or randomized design is also important. The paired cohort design is a design where each man gets both diagnostic tests and in the context of MRI-targeted biopsy is the most typical study design carried out in the literature. Studies with a paired cohort design are more likely to be synthesised separately to studies where a man is randomized to an arm with or without MRI-targeted biopsy, thus details of this are important to report.

The inclusion criteria for the men included in a study are important as they will influence the baseline prevalence of significant cancer in the population being studied. It is known that patients with prior negative biopsy have a lower risk of significant cancer than those with no prior biopsy or those with low risk disease on active surveillance. It is also accepted that the value of MRI-targeted biopsy may vary depending on their prior biopsy status. For example, in men with prior negative TRUS biopsy, it is perhaps intuitive that if they have been referred with ongoing clinical suspicion of prostate cancer, that anterior areas typically missed by TRUS biopsy may be identified by MRI but not by repeat systematic biopsy thus in this context the MRI-targeted biopsy has a greater chance of performing better than the systematic biopsy. Thus, it is essential to report the number of men in a study in each of these different groups of baseline risk.

The MRI-targeted biopsy accuracy will be significantly dependent on the quality of the MRI and its subsequent reporting, thus features allowing the evaluation of the quality of the MRI in a study should be reported. This includes the strength of the magnet, the coils used in the scan, slice thickness and acquisition resolution for T2-weighted imaging and diffusion weighted imaging, the b-values used in diffusion weighted imaging and the temporal resolution used in dynamic contrast enhanced sequences. It is known that using a long b-value for diffusion weighted

imaging is particularly important in identifying significant cancer [67], though it is not clear whether centres are compliant with this, thus it is valuable to report. The temporal resolution during contrast enhanced imaging can determine the image quality for visual inspection. If the temporal resolution is too high, then this can compromise the quality of the image for visual inspection.

The choice of reporting system used is critical as targeted biopsy will only occur at particular thresholds and the scoring system used can make a difference as to whether an MRI lesion is declared as abnormal or not and thus whether or not a patient undergoes targeted biopsy [68]. There was not a particular reporting guideline recommended, highlighting that there was no consensus on a single best scoring system. Though PI-RADS is the most commonly used scoring system, the Likert scoring system has also shown similar performance and is sometime favoured in expert hands, and the consensus process in this study highlighted this [69]. PI-RADS provides well defined and strict rules on scoring and thus is advantageous particularly for less experienced radiologists when learning how to report.

Together with the quality of the MRI conduct, quality of the radiologist's report is particularly important. There is significant inter-observer variability in prostate MRI interpretation and there is a learning curve associated with it, thus it is important to know the experience of the reporting radiologist in the study. Likewise, experience of the clinician performing the biopsy and the pathologist reporting the specimens should be specified.

During the biopsy, there are a number of important biases that can influence performance of the tests being carried out in a paired cohort design. The performance of the test being carried out second can be compromised by prostate swelling and ultrasound degradation from the first biopsy procedure and increased patient discomfort as a procedure continues. On the other hand, needle track marks on the ultrasound could improve the performance of the second procedure if the operator was aware of where the biopsy cores from the first procedure were taken from. Further, if systematic biopsy is being carried out by an operator who has knowledge of where the MRI lesions are, this may

improve the performance of the systematic biopsy as the operator may consciously or sub-consciously alter their procedure based on this information. Therefore, it was agreed that it was important to report the order of the biopsy procedures and whether the operator taking the systematic cores was aware of the MRI information. The method of registration of MRI information during the procedures is also important. Using software to assist a targeted biopsy or performing an in-bore targeted biopsy have quite different economic and practical implications to a visually registered targeted biopsy, thus it is important to report details on registration methods.

To evaluate the role of MRI-targeted biopsy as a replacement test to systematic biopsy, the classification of the results is particularly important. Cancer detection must be divided up by that detected by MRI-targeted biopsy and that detected by standard biopsy. This means that the cores from each of the techniques should be stored separately and it is hoped that in understanding the need to report the separate cancer detection, that investigators will ensure that they communicate this with their theatre team and pathologist. Outcomes for each biopsy technique should be classified by clinically significant, clinically insignificant and no cancer detection (Table 3. 4) which allows an evaluation of the cancer that is detected by both techniques and uniquely to each to be ascertained so that relative merits can be explored.

Of note, there was much debate about what constituted clinically significant cancer by MRI-targeted biopsy. We were not able to agree on one single definition and agreed that further research was needed in this area. We agreed that classical definitions of clinically significant cancer detected by TRUS biopsy (Esptein, Wolters, Goto) would not necessarily apply to MRI-targeted biopsy [70-72]. This was because in MRI-targeted biopsy, one is deliberately sampling an MRI lesion thus may be more likely to get a representative sample through the focal point of the cancer whereas in TRUS biopsy, the systematic sampling error might lead to the same cancer appearing to have a shorter cancer core length [73]. The total cancer core length, often used to determine prognosis in TRUS biopsy may not be as useful in MRI-targeted biopsy as the total cancer core length is dependent on how many targeted cores are taken. Thus, it is

conceivable that whilst MRI-targeted biopsy in a particular man may have identified a higher grade or longer length of cancer, this cancer may have a different prognosis to the same grade or length of cancer that would have been identified by a TRUS biopsy [73].

Some of the strengths of this study include the choice of consensus methodology. RAND/UCLA RAM appropriateness method has advantages of the two-stage approach, allowing reconsideration of each item by the panellists after an informed discussion on the topic. The wider group have an input into the design of the statements to be scored thus every panellist had an equal say on the domains to be covered. The scoring in both rounds is anonymous which allows panellists to express their true opinions. The chair of the round 2 face to face scoring was an experienced epidemiologist, without conflict of interest, who had chaired consensus meetings before. This meant that the discussions within the meeting were focussed on the key methodological aspects of the subject area and that the outcomes of the meeting were less likely to be biased on personal opinion or personal practices on the subject area.

Although this is the case, it is worthwhile discussing some limitations of the study. It is acknowledged that consensus methodology itself is of a low strength of evidence and the conclusions of the work are limited to the opinions of the panellists who comprise the panel. However, we did focus on inviting panellists who were internationally renowned experts in prostate cancer, with publication history in MRI of the prostate or MRI-targeted biopsy. Further, a spread of panellists from the Europe, Asia and North America and from the key disciplines of radiology, urology, histopathology and methodology were invited, thus representing views from a range of different settings and the opinions gauged were likely to be of value. Further, in the context of creating reporting standards, consensus methodology is accepted as being one of the standard ways of deriving these and many landmark reporting guidelines in related [46, 65] and other [11] areas are created with this methodology. Despite the scoring being anonymous, the discussion is not, and it is acknowledged that dominant personalities can dictate the discussion and influence the other panellists. However, our independent chair and anonymous scoring reduced the chances of

this being an issue. The START guidelines are not a static set of recommendations. It is acknowledged that with further understanding of the technique that these guidelines may evolve and in the future another consensus meeting is possible to refine them.

In conclusion, this study established reporting standards for studies of MRI-targeted biopsy of the prostate and derived a START checklist which can be used as a guide for essential items to be included by investigators. This work aims to improve the quality of reporting in the MRI-targeted biopsy literature and allow synthesis and meta-analysis of such data so that the role of MRI-targeted biopsy in the diagnosis of prostate cancer, in relation to systematic biopsy, can be evaluated.

3.5 Statement of contribution

My personal contribution to this work is as follows:

- Study design: I applied the UCLA/RAND methodology to our particular research area. After liaison with one of the creators of the UCLA/RAND methodology, Steven J. Berstein, I customised the study design to fit our purposes.
- Acquisition of data: I was one of the 2 main people responsible for creation of the items for discussion. I created the documents containing the items and amalgamated suggestions from others. I sent out the documents to the panellists for their responses in round 1 and gathered their answers. I liaised with the funder and host institution in New York to arrange presentation of the round 2 items in booklet form. I created the summary graphs for each item and had them ready for presentation form at the round 2 meeting. I was one of the 4 people who transcribed the responses in round 2 to a database for analysis.
- Statistical analysis: I performed the statistical analysis for this study.
- Analysis and interpretation of data: I was one of the two main people responsible for analysis and interpretation of the data.

Other key contributions to this work:

- My supervisors Caroline M Moore and Mark Emberton came up with the concept for the study. Caroline M Moore contributed critically in key study aspects: the study design, acquisition of data, analysis and interpretation of the data and obtaining funding for the work.
- My supervisor Jan van der Meulen was the chair of the consensus meeting.
- The START consortium, named in Table 3. 1 and listed with their affiliation, included the panellists who took part in the consensus meeting. They contributed to interpretation of the data for the publication, though none contributed directly to the writing of this thesis chapter
- I would like to acknowledge Pelican Cancer Foundation and in particular its CEO, Sarah Crane, for funding the consensus meeting and assisting with practical arrangements.
- I would like to thank Samir Taneja and New York University Langone Medical Centre who provided the venue and facilities for the round 2 meeting

3.6 Related Publication

Moore CM*, Kasivisvanathan V*, Eggener S, Emberton M, Futterer JJ, Gill IS, Grubb Iii RL, Hadaschik B, Klotz L, Margolis DJ, Marks LS, Melamed J, Oto A, Palmer SL, Pinto P, Puech P, Punwani S, Rosenkrantz AB, Schoots IG, Simon R, Taneja SS, Turkbey B, Ukimura O, van der Meulen J, Villers A, Watanabe Y, Consortium S.

Standards of Reporting for MRI-targeted Biopsy Studies (START) of the Prostate: Recommendations from an International Working Group.

Eur Urol. 2013;64(4):544-52.

*Joint first author

Chapter 4 Designing a study to change the standard of care from TRUS biopsy to MRI-Targeted biopsy

The findings from the work in this chapter have been published in *The British Medical Journal Open* [74].

4.1 Introduction

The potential for MRI-targeted biopsy to be a replacement test to systematic biopsy was demonstrated in Chapter 2 in a single institution setting. Standardisation of terminology and reporting of MRI-targeted biopsy was described in Chapter 3. TRUS biopsy, due to its historical role in prostate cancer diagnosis as described in Section 1.4 and due to its wide availability, is the most common standard of care for the diagnosis of prostate cancer worldwide [75]. One million prostate biopsies are carried out in the USA and Europe every year [21]. We know that there are limitations with TRUS biopsy due to random and systematic error associated with the technique (Section 1.6). Thus, research has focussed on trying to improve the diagnostic test used to diagnose prostate cancer.

Reviewing the literature on studies comparing MRI-targeted biopsy to TRUS biopsy demonstrated that MRI-targeted biopsy detected a similar amount of significant cancer to TRUS biopsy (236/255 (43%) versus 237/555 (43%), respectively), with fewer cores required (mean of 4 versus 12 cores) [51]. In the MRI-targeted approach, a third of men avoided biopsy and 53/555 (10%) of men avoided the detection of clinically insignificant cancer [51]. The majority of the studies in the literature however were single centre studies and limitations in study quality limited the ability to draw firm conclusions from the synthesis of data from them. Further, it was evident that despite emerging evidence of the role of MRI-targeted biopsy, that the standard of care still remained as TRUS biopsy [75]. There was therefore a need for a robust multi-centre study evaluating MRI-targeted biopsy compared to TRUS biopsy in the detection of clinically significant cancer to help establish the role of MRI-targeted biopsy in prostate cancer diagnosis.

Amongst the START Consortium (Chapter 3), having agreed on reporting standards and consolidated common terminology in MRI-targeted biopsy, we considered various designs for such a study that would be able to change clinical practice and be carried out in a multi-centre setting amongst institutions in the group. This Chapter focuses on the design of the study that was developed from the initial discussions. Chapter 5 focusses on the results of the study that was carried out. The short title of the study that was developed was PRostate Evaluation for Clinically Important disease: Sampling using Image-guidance Or Not? (PRECISION).

4.2 Study design considerations

Two main types of study designs are typically used in diagnostic test evaluation, the first being a paired cohort design; the second being a randomized design. Each has advantages and disadvantages which will be discussed in the following section. In both cases, in the ideal setting, each man would undergo a reference diagnostic test in addition to at least one of the diagnostic test strategies under investigation (index test), in order to establish the diagnostic performance of the index diagnostic test. A reference test is typically a detailed test which is used to determine whether or not an individual patient has the disease. However, as discussed in Section 3.1, there is no ideal reference test in prostate cancer diagnosis.

Although a detailed test, radical prostatectomy specimens would not be a valid choice of reference standard. A reference test is one that should be carried out in all men, regardless of the outcome of the index test. However, radical prostatectomy is only carried out in a small proportion of suitable men diagnosed with the disease on the index test. Not all men with the disease have radical prostatectomy due to other treatment options such as radiotherapy, hormone treatment and active surveillance. Thus, there would not be any men who would be negative for disease on the index tests who subsequently underwent a radical prostatectomy, but as one can see from a 2 x 2 table used to calculate diagnostic test performance (Table 4. 1), this is essential.

Table 4. 1: A typical 2 x 2 table used to calculate diagnostic test performance

An appropriate reference standard would be one in which all patients who undergo the index test also undergo the reference test. The reference test needs to carried out regardless of whether or not the index test (e.g. MRI-targeted biopsy) is positive or negative for cancer. In prostate cancer, there is no ideal reference test since most candidate reference tests are carried out depending on the result of the index test thus typically there are no men who test negative on the index test who go on to have the reference test.

		Reference test	
		Disease positive	Disease negative
Index test	Test positive	a	b
	Test negative	c	d

Sensitivity = a / (a+c); Specificity = d / (b+d);
Positive predictive value = a / (a+b); Negative predictive value = d / (c+d)

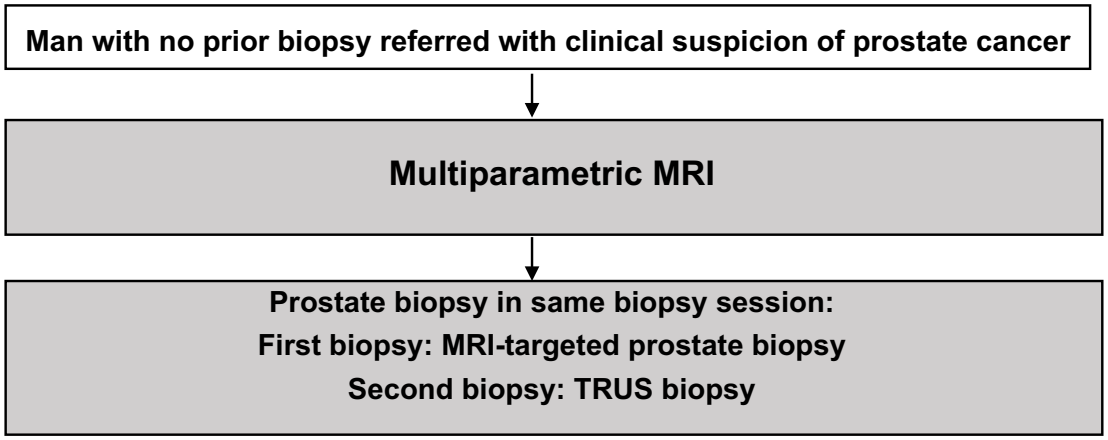
One potential reference test that has been proposed would be a 5mm transperineal template mapping biopsy (see Section 1.7). However, even this test misses some prostate cancer, as demonstrated by the cases of cancer identified by TRUS biopsy but missed by template mapping biopsy in the PROMIS study. Following our institution's publication of the PROMIS study, due to the burden that a full 5mm template mapping biopsy had on patients and the high side effect profile reported [25], there are genuine ethical concerns over the suitability of such a detailed test being carried out in a cohort of men again, thus carrying out a study with this reference standard would be challenging ethically and practically.

Therefore, study designs to evaluate MRI-targeted biopsy compared to TRUS biopsy typically compare the amount of cancer detected by each technique without a true reference standard and take one of the following forms:

4.2.1 Paired cohort design

In this design, each man with suspected prostate cancer undergoes both MRI-targeted biopsy and TRUS biopsy in the same biopsy session (Figure 4. 1).

Figure 4. 1: Paired cohort design study comparing MRI-targeted biopsy to TRUS biopsy



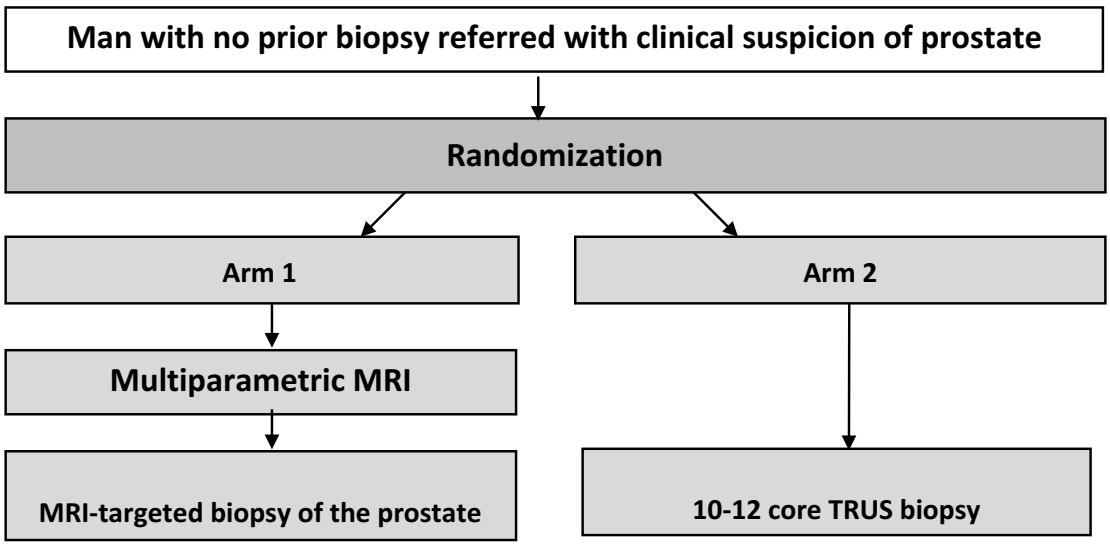
The biopsy cores from each technique need to be stored separately for cancer detection by each technique to be derived, as described in Chapter 3. A direct comparison of the proportion of men with cancer detected by each technique can carried out. Advantages of this design are that as each man serves as his own control, the power of the study is greater than a parallel group randomized study thus fewer men are required for a paired cohort design. In addition, as investigators tend to get reassurance from oversampling of the prostate, it is easier to convince investigators to add the additional test of MRI-targeted biopsy onto their existing test of TRUS biopsy than it would be to ask them to do only one test or the other as might be the case in a randomized design. It is also easier to recruit patients to a study where they get both tests than when they get one test or the other because of the uncertainty associated with only getting one test when outside of the study they could get both. Thus, these factors mean that a paired cohort design in this area is more feasible to run than a randomized study.

There are some disadvantages to this study design. When both tests are carried out in the same patient, the performance of one test can influence the performance of the other, as described in Section 3.4. For instance, if the same operator took both the MRI-targeted biopsy cores and the TRUS biopsy cores, the performance of the TRUS biopsy may be consciously or sub-consciously influenced by MRI-information. This might lead to the TRUS biopsy detecting more or less cancer than if the operator was unaware of such information. Another example would be that it is feasible that the MRI-targeted biopsy procedure leads to needle track marks visible on the ultrasound which may consciously or sub-consciously influence where the TRUS biopsy cores are taken from thus lead to more or less cancer being detected by the TRUS biopsy than if the TRUS biopsy was performed first. Furthermore, a more intensive biopsy strategy combining both tests is more likely to increase the proportion of men with clinically insignificant cancer diagnosed, which is an undesirable outcome.

4.3 Randomized trial design comparing MRI-targeted to TRUS biopsy

In this design, men can be randomized to one of two arms. One arm contains MRI and the other contains TRUS biopsy only (Figure 4. 2).

Figure 4. 2: Randomized study design comparing MRI-targeted to TRUS biopsy



In Arm 2, men can undergo TRUS biopsy as would be the case if MRI were not involved in the diagnostic pathway. In Arm 1, men can undergo an MRI followed by MRI-targeted biopsy. A direct comparison of the proportion of men in each arm with cancer can be carried out. Due to the randomization, one would assume that the proportion of men with cancer in each arm is the same and any differences would be explained by the diagnostic test used in that arm. Advantages of this study design are that the performance bias seen with the paired cohort design is mitigated as men only undergo one biopsy test or the other. Randomization may lead to the presence of known and unknown confounders to be equally distributed between arms. Randomization also allows the acceptability of the diagnostic pathway to be considered. For example, whether patients would be willing to undergo a diagnostic test (if they weren't they would not agree to take part and be randomized or they might withdraw after randomization but prior to receiving the test) and what the reasons for their withdrawals were. This allows the feasibility of adopting this diagnostic test in clinical practice to be evaluated. With a paired cohort design, since both tests are carried out in the same patient, the differential acceptability of the two tests is not easy to elucidate.

Uncertainties exist in the randomized design. In the MRI arm, if the MRI is non-suspicious, should men undergo a systematic biopsy or should they avoid a biopsy? If the MRI is suspicious, should men undergo a targeted biopsy only? Would clinicians and patients be willing to forego biopsies altogether after a non-suspicious MRI and be comfortable with only MRI-targeted biopsies after a suspicious MRI? This study design offers the opportunity to explore these uncertainties. The paired cohort design is a more feasible study design to deliver, and thus has been the chosen design by the majority of the studies in the literature thus far [51, 59]. However, it had not led to a change in practice from TRUS biopsy to MRI-targeted biopsy despite the clinical outcomes of these studies demonstrating advantages of the MRI-targeted pathway. Thus, it was felt that a randomized design may be required to provide the evidence required to change practice. The advantages in reducing performance bias and ability to evaluate the acceptability of the proposed diagnostic pathway were seen to

outweigh the statistical advantages and practicality of running a study with a paired cohort design. The details of the chosen full study design are given below.

4.4 Full study title

A multicentre randomised controlled trial assessing whether magnetic resonance imaging-targeted biopsy is non-inferior to standard transrectal ultrasound guided biopsy for the diagnosis of clinically significant prostate cancer in men without prior biopsy.

4.5 Study objectives

4.5.1 Primary objective

To determine the proportion of men with clinically significant cancer (Gleason grade 3+4 or greater) detected by MRI-targeted biopsy and by TRUS biopsy

4.5.2 Key secondary objectives

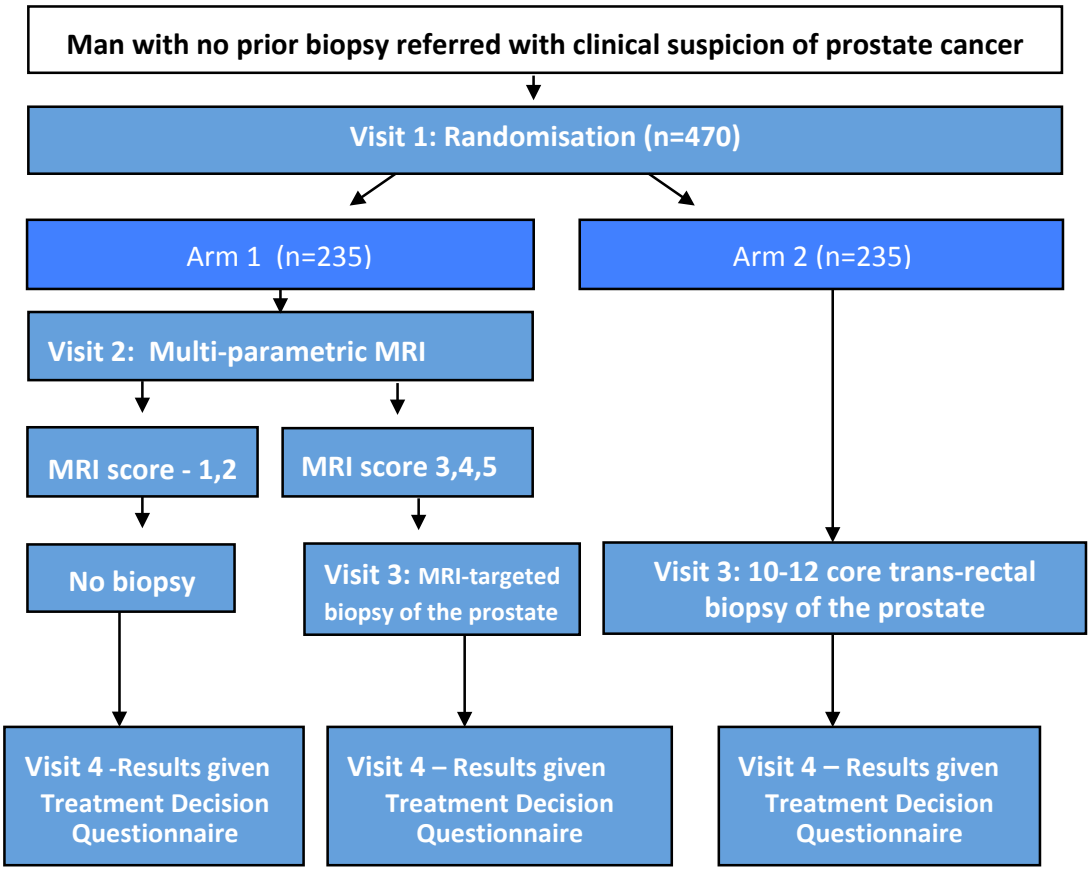
1. To determine the proportion of men with clinically insignificant cancer (Gleason grade 3+3) detected by MRI-targeted biopsy and by TRUS biopsy
2. To determine the proportion of men in the MRI arm who avoid prostate biopsy
3. To determine the proportion of men with post-biopsy adverse events

4.6 Trial Design

PRECISION is a multicenter parallel group randomized controlled trial. Men are randomized to MRI or to TRUS biopsy (Figure 4. 3). This is the first trial to randomize men to an MRI arm in which only MRI-targeted biopsy is carried out in the presence of an MRI lesion (i.e. without any systematic cores) and in which no biopsy is carried out if the MRI is non-suspicious.

Figure 4. 3: PRECISION Trial Schema

Reproduced with permission from [74].



4.7 Setting

This is an international study with institutions from Europe, North America and South America taking part. Institutions that have capabilities of performing MRI-targeted biopsy and TRUS biopsy can take part in the study. Institutions may or may not be from the START Consortium [63]. It is our intention that institutions outside of this group be permitted to take part following approval by the Chief Investigator. Chief Investigator approval is given following review of the institution's previous prostate biopsy detection rates.

4.8 Inclusion criteria

Patients can be included if the fulfil the following inclusion criteria:

1. Men at least 18 years of age referred with clinical suspicion of prostate cancer who have been advised to have a prostate biopsy

2. Serum PSA ≤ 20ng/ml

3. Suspected stage ≤ T2 on rectal examination (organ-confined prostate cancer)

4. Fit to undergo all procedures listed in protocol

5. Able to provide written informed consent

4.9 Exclusion criteria

To be eligible, patients should not have any of the following exclusion criteria:

1. Prior prostate biopsy

2. Prior treatment for prostate cancer

3. Contraindication to MRI (e.g. claustrophobia, pacemaker, estimated GFR ≤ 50mls/min)

4. Contraindication to prostate biopsy

5. Men in whom artifact would reduce the quality of the MRI

6. Previous hip replacement surgery, metallic hip replacement or extensive pelvic orthopaedic metal work

7. Unfit to undergo any procedures listed in protocol

A decision to include men who are biopsy naïve and whom have not been investigated before was taken in order to investigate the group in whom a change of practice in the initial diagnostic pathway would be most impactful. I also wanted to focus on men who at presentation were most likely to have localized

prostate cancer in whom performance of the test would most likely to be discriminatory. In clinical practice, one ideally wants to identify men at the stage at which they have potentially curable, localized disease hence the eligibility criteria were felt to be generalizable. Men with metalwork or contraindications to biopsy or MRI would not routinely undergo MRI in clinical practice, thus these men were excluded.

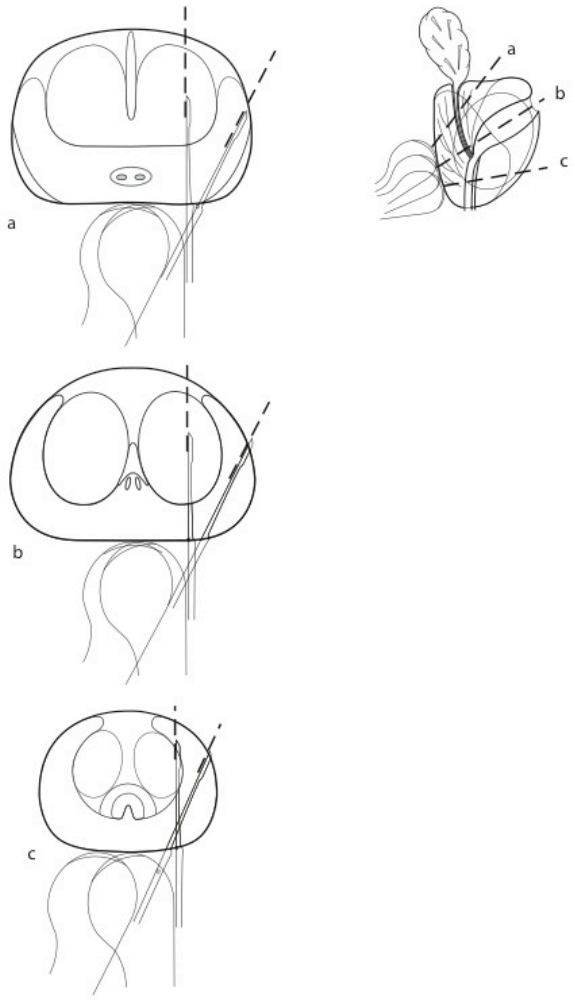
4.10 Interventions

4.10.1 TRUS biopsy arm

Men will undergo a standard 10-12 core TRUS biopsy [52, 75] (Figure 4. 4). With the patient in left lateral position, cores will be taken from the peripheral zone of the base, mid gland and apex of each side of the prostate.

Figure 4. 4: Example of TRUS biopsy technique

Reproduced, with permission, from [52], Wiley-Blackwell ©. The diagram shows 12 biopsies performed under ultrasound guidance with an endfire probe. On the left side of the diagram are the 3 axial views with the trajectories of the lateral and medial core marked on the base of prostate (a), mid-gland of prostate (b) and apex of prostate (c); on the right side of the diagram is the sagittal view with the same trajectories marked on.



4.10.2 MRI arm

Patients will undergo a multi-parametric MRI including T2-weighted, diffusion-weighted imaging and dynamic contrast enhanced imaging. MRIs can be carried out on either a 1.5 or 3.0 Tesla MRI scanner, as these are the typical scanners available in clinical practice. Scans should be conducted as per minimum consensus meeting standards [46].

A radiologist experienced in prostate MRI should report the MRI using PIRADSv2 guidelines. Each suspicious lesion will be given a score of 1-5 and the highest score will correspond to the overall score for a patient. The 1-5 score as described in Table 1. 3 will be as follows [74]:

1 = Highly unlikely to be clinically significant cancer

2 = Unlikely to be clinically significant cancer

3 = The presence of clinically significant cancer is equivocal

4 = Likely to be clinically significant cancer

5 = Highly likely to be clinically significant cancer

Patients with a prostate scoring 1 or 2 will not undergo biopsy. Patients with a prostate scoring 3, 4 or 5 will undergo MRI-targeted biopsy. An operator conducting MRI-targeted biopsy will be experienced in the technique. Up to 3 suspicious areas will be targeted with up to 4 cores per suspicious area taken. Since the registration technique (i.e. visual registration or software-assisted fusion) varies amongst institutions and the access route (i.e. transrectal or transperineal) also varies, institutions will be allowed to use the technique and access route that they have local expertise in.

The experience of clinicians involved in the study at the start of the study will be recorded prior to permission being granted for institutions to open the study locally.

4.10.3 Patient-reported outcome measures

Health related quality of life EQ-5D-5L questionnaires will be completed by participants at baseline on enrollment, 24 hours following MRI, 24 hours following biopsy and 30 days following intervention. In addition, patients will complete post-biopsy and post-MRI side effect questionnaires straight after the intervention and at 30 days following the intervention.

4.11 Treatment Decision

A local clinician reviews the results of the protocol interventions with the patient and makes a decision with the patient on further management according to local standard of care. This may involve discharge of the patient back to the general practitioner, further PSA monitoring, further imaging or biopsy tests or definitive treatment.

4.12 Primary outcome

Proportion of men with clinically significant cancer detected.

If a single core of tissue from prostate biopsy contains Gleason 3+4 or greater cancer, this will be considered clinically significant cancer. This will be assessed when the histology results are reported by the pathologist, which is expected within 30 days of the biopsy.

4.13 Secondary outcomes

Secondary outcomes are listed below in Table 4. 2.

Table 4. 2: Secondary outcomes of the PRECISION study

Reproduced, with permission, from [74].

Outcome	Time frame for assessment
Proportion of men with clinically insignificant cancer (Gleason grade 3+3) detected	When histology results available, at an expected average of 30 days post-intervention
Proportion of men in MPMRI arm who avoid biopsy	When MRI results available, at an expected average of 30 days post-MRI
Proportion of men in whom MPMRI score for suspicion of clinically significant cancer was 3, 4 or 5 but no clinically significant cancer was detected	When histology results available, at an expected average of 30 days post-biopsy
Proportion of men who go on to definitive local treatment (e.g. radical prostatectomy, radiotherapy, brachytherapy) or systemic treatment (e.g. hormone therapy, chemotherapy)	After treatment decision, at an expected average of 30 days post-biopsy
Cancer core length of the most involved biopsy core (maximum cancer core length, mm)	When histology results available, at an expected average of 30 days post-intervention
Proportion of men with post-biopsy adverse events	30 days post-biopsy
Health related quality of life	Baseline, 24 hours post intervention and 30 days post intervention
Proportion Gleason grade upgrading in men undergoing radical prostatectomy	An expected average of 90 days post-biopsy
Cost per diagnosis of cancer	30 days post-biopsy

4.14 Completion of the study

Patients typically will complete the study at the treatment decision visit or when the 30-day questionnaires are completed, whichever is later. However, if at the treatment decision visit, a decision for a further biopsy or a decision for a radical prostatectomy is made, then the patient ends the study once the pathology results of this further procedure are recorded. Patients do give consent for long term follow up in future ethics-approved studies with linkage to national databases. It is recognized that the MRI-negative group of men will be a particularly important group of men to follow up in this manner.

4.15 Patient withdrawal

Patients are permitted to withdraw from the study for any reason and without prejudice. Data up until their time of withdrawal can be included in the study analysis.

4.16 Hypothesis

A non-inferiority hypothesis will be adopted for the primary outcome of this study: I hypothesize that MRI-targeted biopsy will detect no fewer men with clinically significant cancer.

I chose a non-inferiority hypothesis because of the putative advantages of the MRI-targeted biopsy approach. These include the potential for men in the MRI arm to avoid a biopsy and for more men in the MRI arm to avoid clinically insignificant cancer being diagnosed than in the TRUS biopsy arm. Providing no fewer men with clinically significant cancer are detected by the MRI-targeted biopsy, this would provide evidence supporting the adoption of MRI-targeted biopsy over TRUS biopsy.

4.17 Sample size considerations

Large single institutional series of MRI-targeted biopsy (Chapter 2) have demonstrated a detection rate of 50% of men with clinically significant cancer in the biopsy naïve subgroup (Section 2.3.5). Assuming 20% of men avoid biopsy in the MRI arm, a 50% detection rate in 80% of the patients in the arm would correspond to a 40% detection rate of clinically significant cancer in the MRI arm.

Large single institutional studies of TRUS biopsy in biopsy naïve men have demonstrated a detection rate of clinically significant cancer of 27% [14].

Assuming a detection rate of clinically significant cancer of 40% in the MRI arm, 30% in the TRUS biopsy arm, using a margin of clinical unimportance of 5% decided by consensus, 90% power and 2.5% one-sided alpha, 211 men per arm

will be required. Accounting for 10% drop out, at least 470 men will need to be recruited in the study.

4.18 Timeline for recruitment

Recruitment will occur in the outpatient clinics of the participating sites. Assuming 11 participating sites recruiting 3 men per month it is anticipated that the study will complete recruitment in 26 months, commencing February 2016 and completing in April 2018 (Table 4. 3).

Table 4. 3: Table of anticipated recruitment

Month	0	3	6	9	12	15	18	21	24	27
Number of sites	2	2	3	4	6	8	11	11	11	11
Total recruitment	0	18	36	63	99	153	225	324	423	522

4.19 Randomization processes

The randomization sequence is prepared by an independent UCL Surgical and Interventional Trials Unit member using a dedicated computer program. This member of staff is not involved in patient recruitment and no other individuals with patient contact have access to the randomization sequence. The sequence is designed with permuted blocks of varying size, stratified by centre, with equal allocation of patients to each arm (i.e. 1:1 ratio).

Once a patient has given consent to take part in the study and an authorized staff member has confirmed that a patient meets the eligibility criteria of the study, this staff member will request the allocation of that patient by a web-based system. Only this patient's allocation is revealed at this moment and the staff member will not be aware of the allocation of the next patient.

4.20 Blinding

Since both diagnostic tests are quite different, it will not be possible to blind participants or investigators to which test they will receive.

4.21 Data management

I have created dedicated electronic case report forms (eCRF) with the European Association of Urology Research Foundation MARVIN system (XClinical, Germany). I have created automated validation checks and queries into the eCRFs. Permitted range restrictions for data inputting are programmed into the system so that immediate automated checks and queries are sent to sites when incorrect or incomplete data is entered. Authorized individuals from the PRECISION operations group will also check the data for quality and consistency and pose manual queries to sites where appropriate. Data will be stored by the PRECISION Operations Group for 20 years following the publication of the study.

4.22 Data collection

Authorized investigators and members of their team enter all data electronically on the web-based MARVIN eCRF system. Access to each site's MARVIN system is limited to those granted approval locally with specific username and password protection. I have produced an eCRF user guide for all sites to aid them in using the MARVIN system and completing the eCRFs. There is a demonstration mirror website which mimics the real MARVIN system. Sites are required to confirm in writing that they have practiced entering imaginary patient data in the demonstration website and have access to the user guide before being allowed to use the live MARVIN website. Sites will only be allowed to enter data following a Site Induction Visit attended by site staff. The Surgical and Interventional Trials Unit carries out a full check of local site documents before granting permission to commence the study at that site.

Data from clinical encounters will be recorded by authorized site staff at the appropriate times (Figure 4. 3 and Table 4. 4). Patients will complete validated self-reported questionnaires for post-intervention complications and complete EQ-5D-5L questionnaires for assessing health-related quality of life [76] [77].

Table 4. 4: Participant timeline for data collection in the study

Adapted, with permission, from [74]. Table 4. 4(a) shows the timeline for data collection for men randomized to TRUS biopsy. Table 4. 4(b) shows the timeline for data collection for men randomized to MRI who require an MRI-targeted biopsy. Table 4. 4(c) shows the timeline for men randomized to MRI who have no suspicious areas on MRI and do not require a biopsy.

Table 4. 4 (a)

	Contact with patient				
	Visit 0[λ]	Visit 1	Visit 2	Visit 3	Visit 4
Weeks:	-1	0	1	2	6
Tele-consult	X		Not Required		
Consent		X			
Screening		X			
Randomisation		X			
EQ-5D-5L		X		X	X
Optional urine, blood and semen sample		X			
TRUS-biopsy				X	
Immediate post-biopsy questionnaire				X	
Follow up for results of tests					X
Treatment decision[1]					X
30-day post-biopsy questionnaire					X
SAE		Complete as required at any time following registration			
Withdrawal Form		Complete as required at any time following registration			

[1]After treatment decision men revert to standard of care

[λ]This visit is optional depending on local site referral procedures. It is carried out over the phone at 1 week prior to the first face-to-face visit

Table 4. 4(b).

	Contact with patient				
	Visit 0[λ]	Visit 1	Visit 2	Visit 3	Visit 4
Weeks:	-1	0	1	2	6
Teleconsult	X				
Consent		X			
Screening		X			
Randomisation		X			
EQ-5D-5L		X	X	X	X
Optional urine, blood and semen sample		X			
MRI			X		
MPMRI-Targeted Biopsy				X	
Immediate post MRI Questionnaire			X		
Immediate post-biopsy questionnaire				X	
Follow up for results of tests					X
Treatment decision[1]					X
30-day post-biopsy questionnaire					X
SAE		Complete as required at any time following registration			
Withdrawal Form		Complete as required at any time following registration			

[1]After treatment decision men revert to standard of care

[λ]This visit is optional depending on local site referral procedures. It is carried out over the phone at 1 week prior to the first face-to-face visit

Table 4. 4(c).

	Contact with patient				
	Visit 0[λ]	Visit 1	Visit 2	Visit 3	Visit 4
Weeks:	-1	0	1	2	5
Tele-consult	X			Not required	
Consent		X			
Screening		X			
Randomisation		X			
EQ-5D-5L		X	X		X
Optional urine, blood and semen sample		X			
MRI			X		
Immediate post MRI Questionnaire			X		
Follow up for results of tests					X
Treatment decision[1]					X
30-day post MRI Questionnaire					X
SAE	Complete as required at any time following registration				
Withdrawal Form	Complete as required at any time following registration				

[1]After treatment decision men revert to standard of care

[λ]This visit is optional depending on local site referral procedures. It is carried out over the phone at 1 week prior to the first face-to-face visit

4.23 Statistical analysis

A formal statistical analysis plan shall be finalized with the study statistician prior to completion of the study after approval by the data monitoring and safety committee board. The finalized statistical analysis plan has been published [49] and is reproduced here in adapted format.

Continuous variables will be described using the mean and standard deviation or median and interquartile range. Categorical variables will be described using frequencies and percentages.

4.23.1 Primary outcome analysis

The proportion of men with clinically significant cancer (Gleason 3+4 or greater) in each arm will be evaluated. A cancer diagnosis will only be made histologically. The test strategies being compared are TRUS biopsy or MRI ± targeted biopsy. The primary outcome analysis will be based on an intention to treat population where all men randomized in the study are analyzed (Table 4. 5).

Table 4. 5: Treatment of patients within the intention to treat population

Adapted, with permission from [49]. This table shows how a patient randomized to a particular arm is treated in the analysis dependent on what test they end up receiving in the study for the primary intention to treat analysis. The table demonstrates that all men are analysed according to the arm that they were randomized to and this is not influenced by the test they receive.

MRI-TB = MRI-targeted biopsy

Randomized Arm	Test received	Analysis group
TRUS biopsy	TRUS biopsy	TRUS biopsy
TRUS biopsy	MRI (score 1 or 2) and no biopsy	TRUS biopsy
TRUS biopsy	MRI (score 3, 4 or 5) and MRI-TB	TRUS biopsy
TRUS biopsy	Other	TRUS biopsy
MRI	TRUS biopsy	MRI
MRI	MRI (score 1 or 2) and no biopsy	MRI
MRI	MRI (score 3, 4 or 5) and MRI-TB	MRI
MRI	Other	MRI

If a man received the allocated test as well as another test at a later time, as the numbers within the trial follow up are likely to be very small, only the results of the allocated test will be used for the analysis, though any differences will be described in the main text of the results (Table 4. 6).

Table 4. 6: Treatment of patients within the intention to treat analysis in men who had more than one test

Adapted, with permission from [49]. This table shows how a patient randomized to a particular arm is treated in the intention to treat analysis if they have a second diagnostic test within the follow up period of the study after the treatment decision. Only results from the originally allocated test will be considered in the analysis.

MRI-TB = MRI-targeted biopsy

Randomization arm	**1st test received**	**2nd test received after treatment decision**	**Results used**
TRUS	TRUS biopsy	MRI and/or MRI-TB	TRUS biopsy
TRUS	TRUS biopsy	Other biopsy	TRUS biopsy
MRI	MRI (score 1 or 2) and no biopsy	Other biopsy	MRI
MRI	MRI (score 3,4 or 5) and MRI-TB	TRUS biopsy	MRI-TB
MRI	MRI (score 3,4 or 5) and MRI-TB	Other biopsy	MRI-TB

For the primary outcome analysis, if the lower bound of the two-sided 95% confidence interval for the difference in the proportion of men with clinically significant cancer in the MRI ± targeted biopsy group relative to the TRUS biopsy group is greater than −5%, then MRI ± targeted biopsy would be deemed to be non-inferior to TRUS biopsy. If the lower bound is greater than zero, superiority will be claimed.

For the intention to treat analysis, if the primary outcome is unknown, an assumption of “no cancer” status will be made. The impact of this assumption will be tested by repeating the primary outcome analysis on a modified intention to

treat population. In this population, men whose outcome is unknown will be excluded from the analysis (Table 4. 7, Table 4. 8). A final per protocol sensitivity analysis will be carried out, only including men in their randomized arms if they followed the protocol (Table 4. 7, Table 4. 8). This is because for non-inferiority hypotheses, intention to treat analyses have been shown to lead to smaller treatment differences than a per protocol analyses, thus this sensitivity analysis evaluates the impact of this.

Table 4. 7: How to classify patients for modified intention to treat and per protocol analyses for the TRUS biopsy arm

Adapted, with permission from [49]. This table shows how patients randomized to the TRUS biopsy arm are included or excluded for the modified intention to treat analysis and the per protocol analysis compared to the intention to treat analysis.

ITT = Intention to treat

Randomization arm	Diagnostic test received	Action for ITT analysis	Action for modified ITT	Action for per protocol analysis
TRUS	Other diagnostic test	Include	Include	Exclude
TRUS	MRI (score 1 or 2) and no biopsy	Include	Include	Exclude
TRUS	MRI (score 3, 4 or 5) and MRI-TB	Include	Include	Exclude
TRUS	MRI (score 1 or 2) but still has other biopsy	Include	Include	Exclude
TRUS	MRI (score 3, 4 or 5) but other biopsy	Include	Include	Exclude
TRUS	TRUS biopsy but with deviation in biopsy core number greater than ± 10%	Include	Include	Exclude
TRUS	Withdrawn prior to any fully completed diagnostic test	Include	Exclude	Exclude

Table 4. 8: How to classify patients for modified intention to treat and per protocol analyses for the MRI arm

Adapted, with permission from [49]. This table shows how patients randomized to the MRI arm are included or excluded for the modified intention to treat analysis and the per protocol analysis compared to the intention to treat analysis.

ITT = Intention to treat

Randomisation arm	Diagnostic test received	Action for ITT analysis	Action for modified ITT	Action for per protocol analysis
MRI	TRUS biopsy	Include	Include	Exclude
MRI	Other biopsy test	Include	Include	Exclude
MRI	Attempted but incomplete MRI (e.g. because patient could not tolerate full MRI) followed by TRUS biopsy or other biopsy test	Include	Include	Exclude
MRI	MRI±TB but MRI not multi-parametric (e.g. contrast or diffusion weighted sequences not taken)	Include	Include	Exclude
MRI	MRI (score 3, 4 or 5) and MRI-TB but with deviation in biopsy core number greater than ± 10%	Include	Include	Exclude
MRI	MRI (score 3, 4 or 5) and MRI-TB but with additional biopsy test at same sitting	Include	Include	Exclude
MRI	MRI (score 3, 4 or 5) and MRI-TB but where not all of MRI-suspicious areas were targeted e.g. 3 suspicious areas identified but only 1 targeted	Include	Include	Exclude
MRI	MRI (score 3, 4 or 5) but no biopsy	Include	Exclude	Exclude
MRI	MRI (score 3, 4 or 5) but other type of biopsy	Include	Include	Exclude
MRI	Withdrawn prior to any fully completed diagnostic test	Include	Exclude	Exclude

Randomization was stratified by centre, so 95% confidence intervals will be adjusted for centre by a generalized linear mixed model with clinically significant cancer as the dependent variable, the arm as the independent variable and centre as a random effect. An identity link function with binomial distribution will be used with this model to create an adjusted difference in proportion of men with clinically significant cancer. If there is an imbalance in key baseline characteristics between arms (PSA, age, abnormal digital rectal examination, family history of prostate cancer) then these characteristics will be included in the model. Since these key demographic factors were mandatory reporting items it is not anticipated that there will be missing data for these data thus there are no plans for imputation of missing data for adjustment of the primary outcome.

4.23.2 Secondary outcome analysis

Secondary outcome analyses are exploratory as the study was not powered on basis of these. Secondary outcomes will be analyzed on intention to treat populations using the same methods as the primary outcome analysis, though without adjustment for any prognostic factors. Effect sizes will be calculated and presented with 95% confidence intervals. Key secondary outcome analysis is detailed below.

4.23.2.1 Proportion of men with clinically insignificant cancer detection

Histological results from biopsy will be used to determine the proportion of men with clinically insignificant cancer, defined as Gleason grade 3+3, in each arm.

4.23.2.2 Proportion of men who avoid biopsy in MRI arm

Men scoring 1 or 2 after MRI should not undergo prostate biopsy. The proportion of men in the MRI arm scoring 1 or 2 will be calculated.

4.23.2.3 Cancer core length of the most involved biopsy core

In patient with prostate cancer detected on biopsy, some cores will contain cancer and others will not. The length of cancer in each core will be reported by the pathologist. The core that contains the longest length of cancer is the maximum cancer core length for that patient. The mean maximum cancer core length for each arm will be calculated and compared using mixed effects linear

regression with maximum cancer core length as dependent variable, arm as the independent variable and centre as a random effect.

4.23.2.4 Proportion of men with post-biopsy adverse events

A numerical analogue score is used to capture immediate post-biopsy discomfort and pain. Scores will be summarized for each arm. 30-day post-intervention complications (pain, urinary retention, fever, pain, erectile dysfunction, urinary incontinence, haematuria, blood in the sperm and blood in the sperm) are captured by their presence or absence, duration and severity. The proportion of patients experiencing each complication will be calculated and compared qualitatively between arms.

4.23.2.5 Health-related quality of life scores

Health-related quality of life is captured using EQ-5D-5L questionnaires. Descriptive domain and visual analogue scores from baseline, 24-48 hours post intervention and at 30-days post intervention will be summarized and converted to EQ-5D descriptive scores using the value set for the United Kingdom. Mean differences between arms will be calculated by using a repeated-measures mixed model, adjusting for baseline levels of the outcome variable, taking into account men who fully completed a questionnaire.

4.23.2.6 Proportion of men going onto definitive treatment

At the treatment decision visit, patients can undergo a range of management options at the discretion of the local clinician. The most appropriate option will be recorded. Options include: discharge, PSA monitoring, further investigation, treatment with curative intent, treatment to reduce progression of the disease. Treatments can include and are not limited to active surveillance, radical prostatectomy, radical radiotherapy, focal therapy and androgen deprivation therapy. If appropriate data is available, the proportion of men undergoing types of treatment will be calculated and compared qualitatively between arms.

4.23.2.7 Proportion of Gleason grade upgrading in men undergoing radical prostatectomy

One of the treatment options in either arm is radical prostatectomy. Those undergoing radical prostatectomy have their final Gleason grade pathology

recorded. The proportion of men who have cancer upgraded from biopsy to radical prostatectomy for each arm will be calculated and compared qualitatively.

4.23.2.8 Cost per diagnosis of cancer

Within trial short-run cost-effectiveness will be calculated from an NHS health system perspective including costs of the diagnostic tests, staging tests and health care contacts within 30 days. Costs will be estimated by multiplying standard unit costs (e.g. NHS Reference Costs) by key resource use data captured within the trial. The mean cost per patient per arm and incremental cost per patient for the MRI arm compared to the TRUS biopsy arm will be calculated. The average cost per diagnosis of clinically significant cancer for each arm and incremental cost per additional case of clinically significant cancer diagnosed or clinically insignificant cancer avoided in the MRI arm will be calculated.

4.24 Ethical considerations

National and/or local ethical and governance approvals will be sought prior to opening the study at an institution. In the UK, the National Research Ethics Service Committee East Midlands Leicester gave favourable approval for the study on the 3rd June 2015 (REF: 15/EM/0188).

4.24.1 Identification of patients and consent process

Potential patients for the study are identified by the clinical care team receiving referrals for men with suspected prostate cancer. A patient information sheet will be provided to each participant who will have adequate time to read it, comprehend the information, ask questions about it and weigh up a decision to take part in the study (at least 24 hours given to each patient in the UK). The UK patient information sheet is provided at the end of this chapter. Consent will be taken by staff with appropriate training (e.g. Good Clinical Practice or equivalent training) at a face to face visit. The model consent form is given in Figure 4. 5. There is an optional consent for collection of biological samples (blood, urine, semen) to be stored at the UCL/Royal Free Hospital Biobank for future ethically approved research. This will be obtained if appropriate funding for the storage of the samples is secured prior to the start of the study.

Figure 4. 5: Model consent form for PRECISION Study

Reproduced, with permission, from [49].

(To be presented on local headed paper)

REC Number: 15/EM/0188 Centre Number

Subject Identification Number:

CONSENT FORM

Title of Project PRostate **E**valuation for **C**linically **I**mportant disease: **S**ampling using **I**mage-guidance **O**r **N**ot. (PRECISION)

Name of Researcher:

Please initial box

1. I confirm that I have read and understand the information sheet dated..... (version.....) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from the sponsor of the trial (University College London) and responsible persons authorised by the sponsor, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I agree to my GP being informed of my participation in the study. ☐

5. I agree to take part in the above study. ☐

All boxes above must be initialed for consent to be valid

The following requests are optional, if you do not give permission, you can still participate in the study

6. I agree to giving urine and/or blood and/or semen samples and/or prostate pathology specimens which will be stored and made available for future ethically approved research ☐

7. After I complete my involvement in the study, I give permission for the research team to check my records through the Office of National Statistics and NHS databases and I give permission to be contacted for further information ☐

8. I give permission for my full postal, email address and mobile phone number to be recorded and stored. This will be used for research purposes only and will remain confidential. This information may be used for sending out quality of life questionnaires, if required. ☐

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature
Name of Chief Investigator *(if different to the person taking consent)*	Date	Signature

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

4.24.2 Patient confidentiality

Data stored in the study in the MARVIN eCRFs system is anonymised and linked data. Participants are referred to by a unique study number. The linkage code is securely stored at the local site only. Source documents will be stored securely and archived at the local centre. Data for each patient is only accessible by authorized individuals at that site with usernames and password protected accounts. Authorisation is granted by the local site principle investigator and access is given by the central PRECISION data manager.

4.24.3 Trials Unit coordination of study

Assistance in trial coordination, ensuring that the trial adheres to key governance requirements will be carried out by the UCL Surgical and Interventional Trials Unit. The trial sponsor is University College London (UCL REDA Number: 15/0299) and the UCL Surgical and Interventional Trials Unit has been delegated responsibility to ensure high quality trial conduct on behalf of UCL by the UCL Comprehensive Clinical Trials Unit. The trial has been registered with Clinicaltrials.gov, registration number NCT02380027.

4.24.4 Monitoring of study

A global trial steering committee (GTSC), comprising individuals who are independent to the PRECISION study, monitors and supervises progress of the study towards its overall objectives at regular intervals and consider recommendations of the data monitoring committee.

A data monitoring committee (DMC) comprises an independent chair, clinical representative, patient representative and statistician. The DMC safeguards the interest of the trial participants and monitors the conduct of the trial at regular intervals. The DMC is independent of the GTSC but presents its reports to the GTSC.

4.24.5 Harms to patients and adverse events

TRUS biopsy, MRI and MRI-targeted biopsy are all currently used investigations for men with suspected prostate cancer. As men with suspected cancer would typically undergo a diagnostic test outside of the study anyway, it is not anticipated that additional harms to patients will be experienced by patients taking part in the study. Possible biopsy side effects that are expected include pain, haematuria, haematochezia, haematospermia, dysuria, urinary tract infection, erectile dysfunction. These symptoms tend to be mild and self-limiting. The main possible related risk of note is a 1-4% risk of urosepsis from biopsy. To minimise this risk patient's will only undergo biopsy if there is no suspicion of urinary tract infection on urine dipstick and/or microscopy, culture and sensitivity

of a urine sample. MRI itself is generally safe and is used in everyday practice. Reactions to gadolinium contrast used in MRI have been reported. Mild allergic reactions are present in less than 0.4% and serious reactions are present in less than 0.01% of patients.

As per governance requirements all adverse events and serious adverse events occurring in the study will be recorded. An adverse event is any untoward medical occurrence in a clinical trial subject undergoing any intervention in the trial, which does not necessarily have a causal relationship with this treatment. A serious adverse event is any untoward medical occurrence as a result of any intervention in the trial that results in death, is life-threatening, requires hospitalisation or prolongation of an existing inpatients' hospitalisation or results in persistent or significant disability or incapacity.

A member of the local PRECISION team at an institution must report adverse and serious adverse events on a dedicated eCRF as close to the event happening as possible. Serious adverse events must be reported within 24 hours of knowledge. Generation of the eCRF leads to an automatic notification of the study coordinator, chief investigator and UCL Surgical and Interventional Trials Unit. Adverse event logs are reviewed by the DMC. The Sponsor and/or ethics committee will be notified of any events if required.

4.25 Dissemination

Study results will be presented at local, national and international conferences. Results will be published in peer-reviewed publications and scientific and lay media outlets. Patient support groups will be informed of the results and my contact details will be made available for any queries that patients and public members may have.

4.26 Funding

I was awarded a National Institute for Health Research Doctoral Fellowship for funding of the PRECISION Study (DRF-2014-07-146). Through this funding, I successfully applied for the study to be placed on the NIHR portfolio which

funded local UK sites (UK CRN ID 18902 PRECISION). I also successfully applied for non-UK site funding by the European Association of Urology Research Foundation (EAURF2015001).

4.27 Evaluating the pragmatism of the PRECISION study

The purpose of the study is to provide evidence to support a decision on whether to adopt MRI-targeted biopsy in clinical practice. In order to evaluate whether the intended study design was suitable for this purpose and generalizable to clinical practice, one method of evaluating the pragmatism of the design is by using the Pragmatic Explanatory Continuum Indicator Summary (PRECIS)-2 tool [78]. This tool evaluates the pragmatism of the study in nine domains, including eligibility criteria, recruitment, setting, organisation, flexibility in delivery, flexibility in adherence, follow up, primary outcome and primary analysis. Each domain is scored subjectively from 1 (very explanatory) to 5 (very pragmatic) and can be represented on a summative pictorial diagram. With respect to the individual domains, the scores assigned for the PRECISION study design are:

i. Eligibility – score 4 (rather pragmatic). The inclusion and exclusion criteria in PRECISION are quite representative of the participants who would receive this intervention if it were part of usual care. The intended patient group includes those with clinical suspicion of prostate cancer based on the typical parameters used in clinical practice (raised PSA or abnormal digital rectal examination) who would typically undergo further investigation. There are some upper limits (e.g. PSA of 20 or less) which were used to rationalise the group of men in whom clinicians would typically investigate further with standard diagnostic test options.
ii. Recruitment – score 5 (very pragmatic). The patients will be recruited from outpatient clinics where men with suspected prostate cancer are seen. This is typically the same setting that men in usual care would be considered for further investigation
iii. Setting - score 4 (rather pragmatic). This will be a multi-centre study in which patients are recruited from hospitals offering prostate cancer diagnostic tests in a range of countries and continents. Non-academic

centres outside of the original working group are permitted to take part. Though the intention is to include non-specialist centres, it is accepted that on average the degree of expertise in the participating centres may be higher than that of the average centre not taking part in the study as is commonly the case with units who volunteer to take part in studies and also because centres were required to present their prior detection rates from prostate biopsy procedures in advance of being given approval to take part.

iv. Organisation – score 3 (equally pragmatic and explanatory). The study centres need to carry out pre-biopsy MRI in one arm, and have clinicians with appropriate expertise to report the MRI and perform the trial procedures. Though no minimum experience level for a specific individual was specified, it is acknowledged that the centres taking part were likely to have clinicians with above average expertise. Thus, should MRI-targeted biopsy be adopted in clinical practice, changes to the organisation of service to allow capacity for pre-biopsy MRI in patients and training in the techniques would be required.

v. Flexibility (delivery) – score 4 (rather pragmatic). The study allows clinicians performing MRI-targeted biopsy to choose the access route and registration technique that they have available to them locally. However, there were some limits set – for example a maximum of 3 suspicious areas to be targeted, with a maximum of 4 biopsy cores per suspicious area. These limits were chosen to mirror clinical practice as closely as possible.

vi. Flexibility (adherence). Since patients with suspected prostate cancer recommended to undergo a diagnostic test are likely to undergo further investigation, measures to improve adherence were not included and as per PRECIS-2 guidelines, this domain was not applicable to the study.

vii. Follow up – score 4 (rather pragmatic). The follow up care in the study is similar to usual care. For example, patients in usual care typically get a consultation for discussion of whether diagnostic tests are appropriate for them, a consultation for the MRI and biopsy and a consultation for the results of the diagnostic tests. This is consistent with the follow up in the

study, though there are additional questionnaires that the patient completes following intervention.

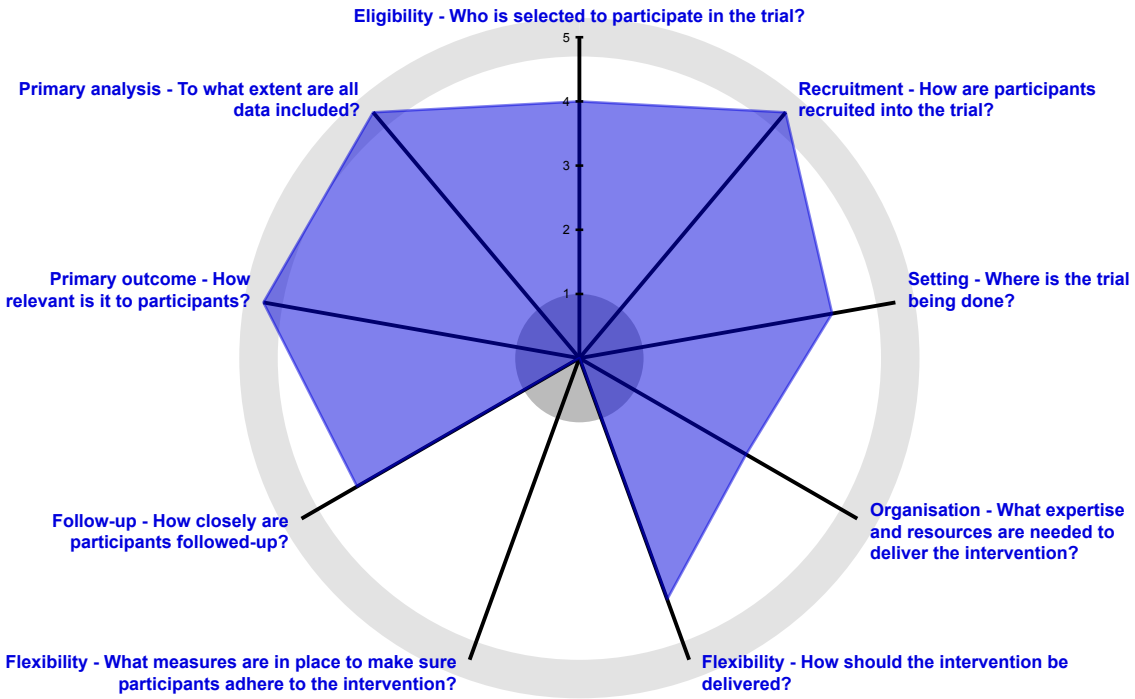
viii. Primary outcome – score 5 (very pragmatic). The primary outcome of clinically significant cancer detection was chosen as it relates to expected prognosis which is one of the most important outcomes for patients.

ix. Primary analysis – score 5 (very pragmatic). The primary analysis is an intention to treat analysis including all randomized patients. A sensitivity analysis using a modified intention-to-treat and a per-protocol sample were also carried out.

Overall, PRECISION scores highly for being a pragmatic study (Figure 4. 6), thus its findings are anticipated to be highly generalizable to clinical practice.

Figure 4. 6: PRECIS-2 diagram showing degree of pragmatism of the PRECISION Trial design

PRECISION is a rather pragmatic study based on the nine domains of the PRECIS-2 tool [78]. The larger the blue shaded area, the more pragmatic the study is.



4.28 Statement of contribution

My personal contribution to the PRECISION Study is as follows:

- Study concept: I contributed to development of the study concept as a member of the START Consortium
- Study design and protocol: I wrote the study protocol
- Ethical approval: I obtained ethical approval for the study
- Funding: I obtained funding for the study
- Database management: I created the MARVIN eCRF content and planned the automated validation and queries
- Trial documents: I created the patient information sheet, consent form and GP letter
- Site recruitment: I recruited sites to the study
- Site initiation: I set up and conducted all 25 site inductions
- Site queries: I responded to all clinical site queries
- Governance: I was co-principle investigator of the study at University College London and was global study coordinator
- Trial progress: I was responsible for ensuring appropriate trial progression at the site level and globally, troubleshooting any issues
- Acquisition of data: I consented patients for the study at University College London and Northwest London Healthcare NHS Trust
- Performance of trial procedures: I performed trial procedures at University College London
- Study visits: I oversaw study visits for patients at University College London
- Statistical analysis: I formulated the initial statistical analysis plan and recruited a specialist statistical unit to finalise the statistical analysis plan and perform statistical analysis
- Interpretation of data and writing of work from PRECISION. I was the main individual responsible for interpretation of data and writing up of work.
- Health economic analysis: I performed health economic analysis

Other key contributions to the PRECISION Study:

- My supervisors Mark Emberton and Caroline Moore were Chief Investigators of the study and gave critical input into the study design, key aspects of trial conduct and results interpretation.
- The START consortium contributed to development of the study design and provided input into interpretation of the data, though did not directly contribute to the writing of this chapter
- The local Principle Investigators were responsible for obtaining local approvals to start the study at their institution and for recruiting their patients at their site
- The study teams at the local sites were responsible for study visits, performing procedures and completing the eCRFs at their site
- Fatima Jichi, Richard Simon, Yemisi Takwoingi and Jon Deeks were responsible for finalizing the statistical analysis plan and conducting the statistical analysis of the study
- Steven Morris and Sarah Willis assisted with the planning and conduct of the Health Economic Analysis of the study
- Clare Allen and Francesco Giganti performed MRI quality control
- Alex Freeman, Marzena Ratynska, Charles Jameson, Imen Ben-Salha and Aiman Haider performed quality control of the pathology data
- The UCL Surgical and Interventional Trials Unit assisted with study coordination and provided oversight for the trial on behalf of UCL, the study sponsor. Specific individuals involved were Chris-Brew Graves, Samim Patel, Ingrid Potyka, Neil McCartan, Cinzia Baldini and Jack Grierson.
- Patrick Magill, David Elkin and Norman R. Williams were members of the Data Monitoring Committee
- Christien Caris and Joke van Egmond helped with the programming in the creation and maintenance of the MARVIN eCRF database.

4.29 Related Publication

Kasivisvanathan V, Jichi F, Klotz L, Villers A, Taneja SS, Punwani S, Freeman A, Emberton M, Moore CM.

A multicentre randomised controlled trial assessing whether MRI-targeted biopsy is non-inferior to standard transrectal ultrasound guided biopsy for the diagnosis of clinically significant prostate cancer in men without prior biopsy: a study protocol.

BMJ Open. 2017;7(10):e017863.

Chapter 4: Additional information: Patient information sheet for PRECISION study

Version 1.2, 26th August 2015

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

Study Short Title:
PRostate Evaluation for Clinically Important disease: Sampling using Image-guidance Or Not

Study acronym:
PRECISION

[redacted]

UCL Reference number: 15/0299

REC Reference number: 15/EM/0188

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

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

Ask us if there is anything that is not clear. You will have at least 24 hours to decide whether or not to take part but take as much time as you need to consider the study.

Part 1

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

What is the purpose of the study?
The standard way of diagnosing prostate cancer is to carry out a trans-rectal ultrasound guided (TRUS) biopsy. This involves inserting an ultrasound probe into the back passage after which 10-12 pieces of tissue are taken from the prostate from areas in the prostate most likely to contain cancer. Another way of doing a biopsy is to perform an MRI scan of the prostate on an earlier day and use that information to help take the biopsies. If there is a suspicious area in the prostate on the MRI, a few biopsies can be directed at where the suspicious area is thought to be, also using a probe in the back passage. Up to 12 pieces of tissue can be taken. If there is no suspicious area on the MRI, which occurs in about 30% of men, then no biopsy will be taken at all.

We currently do not know for certain whether using MRI directed biopsies will allow us to detect the same, more or less prostate cancer than if we do not use MRI. Current evidence supports the idea that using MRI directed biopsies may detect a similar amount of cancer to when it is not used but one advantage is it may allow a man to avoid a biopsy.

The main purpose of this study is to assess whether MRI-targeted biopsy can detect a similar amount of cancer as 10-12-core TRUS biopsy.

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

What are the benefits to me of taking part in this study?
You will benefit by having the diagnostic test that will help us establish whether or not you have prostate cancer. The research team will ensure your tests are carried out as quickly as possible and will be a point of contact for you should you have any concerns or questions.

If you are required to have an MRI (50% of participants) then there is a chance (up to 30%) that you could avoid a biopsy and its risks altogether if the MRI is normal.

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

1. What type of study is this?

This is a randomised study – Sometimes we don‘t know which way of investigating patients is best. To find out, we need to compare different tests. We put people into groups and give each group a different diagnostic test. The results are compared to see if one is better. To try to make sure the groups are the same to start with, each patient is put into a group by chance (randomly).

You will be required to attend a screening visit with a member of the research team who will spend around 40 minutes explaining what is involved in the study and making sure you are eligible for the study. You will be asked to fill out a short questionnaire.

You will then be randomly allocated to one of two groups. One group will receive a TRUS-biopsy and the other group will receive an MRI before the doctors decide on whether to perform a biopsy or not. If a biopsy is required after the MRI then it will be carried out taking into account information from the MRI.

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

In this study you will asked to visit the hospital 3-4 times in total depending on which group you are allocated to. This is a similar number of times to if you were not taking part in the study.

If you are assigned to the TRUS-biopsy group you will then undergo the TRUS-biopsy approximately at 2 weeks following the screening visit. The procedure itself takes about 40 minutes and is usually carried out under local anaesthetic. Typically 12 cores are taken. We wait for the results and discuss treatment options with you in clinic at around 2-3 weeks after the biopsies. You will be required to fill out questionnaires after the biopsies and at 30 days after the biopsies. The questionnaires should take about 10 minutes to fill out and you can post them back to us. You may be reminded to fill the questionnaires out by a phone call from the research team.

If you are assigned to the MRI group, you will have an MRI at about 2-3 weeks of the screening visit. The MRI takes about 40 minutes. You will need to fill in a questionnaire after this. If you have an MRI with a high enough suspicion (MRI Score 3, 4 or 5) you will be booked for a biopsy following the MRI.

The biopsy procedure itself takes about 40 minutes and is usually carried out under local anaesthetic. A maximum of 12 cores will be taken but this may be fewer. It will be carried out using the MRI scan to influence where the biopsies are taken from. Software may be used to transfer additional information from the original MRI onto the screen when the biopsies are taken.

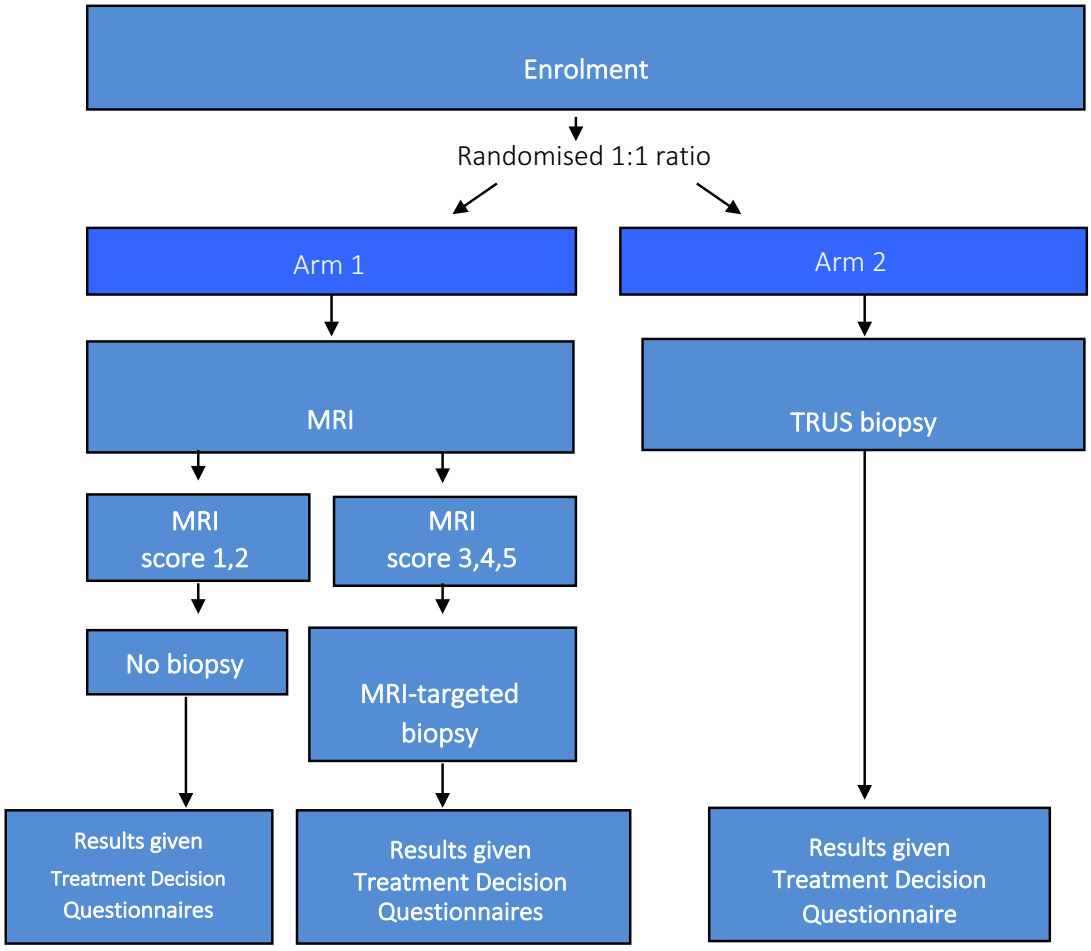
We then wait for the results and discuss treatment options with you for 30 minutes in clinic approximately at 2-3 weeks after the biopsies. You will be required to fill out a questionnaire after the biopsies and at 30 days after the biopsies. If you do not need a biopsy then we will explain this to you approximately 2 weeks following your MRI and you will need to complete a questionnaire 30 days after the MRI. You may be reminded to fill the questionnaires out by a phone call from the research team. You can post these questionnaires back to us.

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

As an additional option you will be asked at the consent and screening visit if you are happy to provide urine, semen and blood samples which will be stored for future research studies looking into identifying markers within these substances that can help us diagnose prostate cancer better. You will also be asked if the prostate tissue from your biopsies, after they have been analysed for your care, can be stored for these future research studies. This is optional and not a necessity to take part in the study.

Being involved in the study does not limit subsequent tests or treatment you may receive. If you do undergo further tests or treatment after the study is complete we may check the results of these on your records. After completing the study, we also ask your permission to check your health through national databases. All information which is collected about you during the course of the research will be kept strictly confidential, and any information about you which leaves the hospital will have your name and address removed so that you cannot be recognised. Please see Part 2 for further information on this.

Study Schema:



3. What will I have to do?

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

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

You will be required to fill out questionnaires immediately after the biopsies and during follow up. You should attend your follow up clinic appointment where we discuss your results. Treatment options will be discussed with you at the results clinic. In total you will be required to attend the hospital 3-4 times.

4. What are the alternatives for diagnosis?

The diagnosis of prostate disease usually requires a prostate biopsy. All prostate biopsies involve the use of a biopsy device to take samples from the prostate gland. MRI is an additional test to help diagnose prostate cancer. If an MRI shows a suspicious area, biopsies will still be required to diagnose prostate cancer. If an MRI does not show a suspicious area, in some cases men may be able to avoid a biopsy.

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

Being involved in the study puts the participants at no additional risk than if they were not involved in the study but underwent the normal procedures for men referred for further investigation of prostate disease.

Risks of prostate biopsy include:

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

Risks of MRI include:

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

It is not known which of the two biopsy techniques (TRUS-biopsy or MRI-targeted biopsy) is more effective, though current evidence suggests that they are similar. Both biopsy techniques are used routinely in everyday clinical practice.

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

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

If you experience any side effects after biopsy as listed in the 30-day questionnaire please record these in the relevant section in the questionnaire. If you experience any other untoward complication or need to see a doctor we would like to know about this so please let us know on the above number as soon as possible after the complication. For any emergencies at any time or if you are unable to contact a member of the research team, please attend your local accident and emergency for an assessment.

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

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

9. Will my taking part in the study be kept confidential?
Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2.

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

11. Contact Details

If you have any further questions or need any further information please do no hesitate to contact the research team:

This completes Part 1 of the Information Sheet.

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

Part 2

12. What if relevant new information becomes available?

Sometimes we get new information about the procedures being studied. If this happens, we will tell you about it and discuss whether you want to or should continue in the study. If you decide not to carry on, we will make arrangements for your care to continue. If you decide to continue in the study we will ask you to sign an updated consent form.

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

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

14. What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the research team who will do their best to answer your questions (0207 679 9092). You can also contact the Study Coordinator or Chief Investigators on the number or address given earlier in this document. If you wish to complain by other means or have any concerns about any aspect of the way you have been approached or treated by members of staff or about any side effects (adverse events) you may have experienced due to your participation in the clinical study, the normal National Health Service complaints mechanisms are available to you. You can contact the hospital Patient Advice and Liaison Service (PALS) at University College Hospital London on 020 3447 3042. If you have a different local hospital, their PALS number can be found on the NHS Choices Website at http://www.nhs.uk/chq/pages/1082.aspx?CategoryID=68. Further details can also be obtained from the Department of Health website: http://www.dh.gov.uk.

Every care will be taken in the course of this clinical study. However in the unlikely event that you are injured by taking part, compensation may be available. If you suspect that the injury is the result of the Sponsor's (University College London) or the hospital's negligence then you may be able to claim compensation. After discussing with your study doctor, please make the claim in writing to Mrs Caroline Moore who is the Chief Investigator for the clinical study and is based at University College London. The Chief Investigator will then pass the claim to the Sponsor's Insurers, via the Sponsor's office. You may have to bear the costs of the legal action initially, and you should consult a lawyer about this.

Participants may also be able to claim compensation for injury caused by participation in this clinical study without the need to prove negligence on the part of University College London or another party. You should discuss this possibility with your study doctor in the same way as above.

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

If you consent to take part in this study, the records obtained while you are in this study as well as related health records will remain strictly confidential at all times.

The information will be held securely on paper and electronically at your treating hospital under the provisions of the 1998 Data Protection Act. The information will be made available to persons in the clinical and research teams treating you. Your name and personal details will not be passed to anyone else outside the clinical team, research team or the Sponsor, who is not involved in the study. In some cases the research team may verify results of tests at University College London Hospital carried out at your local hospital (for example MRI results or prostate biopsy results).

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

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

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

In line with the regulations, at the end of the study your data will be securely archived for a minimum of 5 years. Arrangements for confidential destruction will then be made.

Anonymised data collected during the study may be transferred for the purpose of processing or analysis to associated researchers within/outside the European Economic Area. Some countries outside Europe may not have laws which protect your privacy to the same extent as the Data Protection Act in the UK or European Law. The Sponsor of the study will take all reasonable steps to protect your privacy.

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

16. Will my GP be informed of my involvement?

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. You will not be able to participate in this study if you do not give us this permission to inform your GP.

17. What will happen to any samples I give?

The majority of samples taken for this study are routinely carried out as part of the investigation of prostate disease. Samples include blood, urine and prostate

tissue. The samples will be analysed and stored at the hospital site that they were carried out at as would normally be done in routine care. In some cases, a member of the research team at University College London Hospital may verify the prostate biopsy results. This is done routinely in clinical practice for some patients where results need to be confirmed by another doctor.

There is the additional option of giving urine, blood and semen samples and prostate tissue samples from biopsies specifically to be stored for future research purposes that are approved by a research ethics committee. These samples will be stored securely at a purpose-built facility. They will not be identifiable to you and you will not be informed if they are used in the future.

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

The results of the study will be available after it finishes and will usually be published in a medical journal or be presented at a scientific conference. The data will be anonymous and it will not be possible to identify you in any report or publication.

Should you wish to see the results, or the publication, please ask your study doctor or visit www.ctgparticipant.org.

19. Who is organising and funding the research?

The study is funded by the National Institute for Health and Research (NIHR) UK. The study coordinator Mr Veeru Kasivisvanathan, is funded by a Doctoral Research Fellowship by the NIHR. The work may form part of his Doctoral Thesis.

20. Who has reviewed the study?

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

21. Further information

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

Site Study Nurse Details:

Principal Investigator (site) details:

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

Prostate Cancer UK – 0800 074 8383 - http://prostatecanceruk.org

Macmillan Cancer Support - 0808 808 0121 – http://www.macmillan.org.uk

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

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

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

Chapter 5 The PRECISION Trial results

5.1 Introduction

The rationale, background, hypothesis and methods of the PRECISION trial are given in Chapter 4. In Chapter 5, I will present the results of the study and discuss the implications of these. The findings from the work in this chapter have been published in *The New England Journal of Medicine* [49].

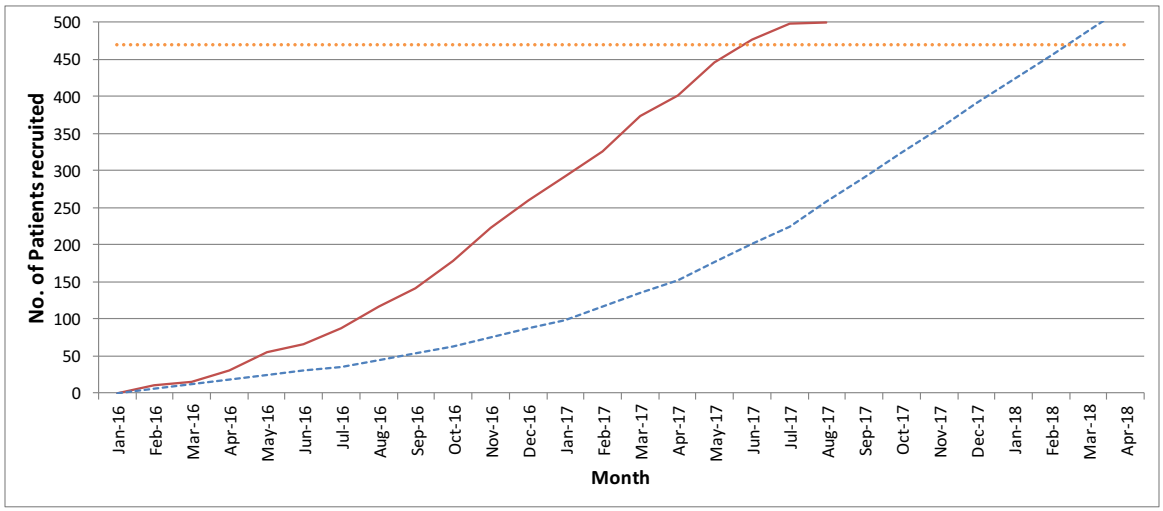
5.2 Results

5.2.1 Study overview

Five hundred men were randomized between February 10th 2016 to August 2nd 2017 to MRI or to TRUS biopsy. Recruitment completed well ahead of schedule (Figure 5. 1).

Figure 5. 1: Recruitment rate in the PRECISION study

The dotted orange line represents the minimum recruitment target of 470 patients. The blue dashed line represents the intended target recruitment rate. The solid red line represents the actual recruitment rate in the study. Recruitment completed within 18 months of commencing recruitment, which was well ahead of schedule.



Two-hundred and fifty-two men were randomized to the MRI arm and 248 men were randomized the TRUS biopsy arm. Recruiting sites were based in Europe (Belgium, Finland, France, Italy, Germany, Netherlands, Switzerland, United Kingdom), North America (Canada, United States of America) and South America (Argentina). The majority of patients were recruited from Europe (73%), followed by North America (14%) and South America (13%) (Table 5. 1).

Table 5. 1: Geographical distribution of recruitment of patients

This table summarises the recruitment of patients by geographical area. MRI±TB = MRI ± targeted biopsy.

Geographical area	MRI±TB, n	TRUS biopsy, n	Total, n (%)
Europe	185	180	373 (73%)
United Kingdom	32	31	63 (13%)
Rest of Europe	153	149	310 (60%)
North America	36	35	71 (14%)
South America	31	33	64 (13%)
Total	**252**	**248**	**500**

Twenty-five sites opened the study and 23 sites randomized patients (Table 5. 2).

Table 5. 2: Sites involved in the PRECISION Trial and their recruitment

25 sites opened the PRECISION study and 23 sites recruited patients. This table gives the total number of patients recruited from each site and how many were randomized into each arm from sites. MRI±TB = MRI ± targeted biopsy. Adapted, with permission from [49].

Centre	MRI±TB	TRUS biopsy	Total
Helsinki University Hospital, Finland	37	37	74
Centro de Urologia CDU, Argentina	31	33	64
Sapienza University, Italy	31	30	61
Mayo clinic, Rochester, Minnesota, USA	27	27	54
Oulu University Hospital, Finland	27	26	53
San Raffaele Hospital, Italy	26	25	51
University College London Hospitals NHS Foundation Trust, UK	10	11	21
Martini Klinik, Hamburg, Germany	10	10	20
London North West Healthcare NHS Trust, UK	7	6	13
Erasmus University Medical Center, Rotterdam, the Netherlands	6	6	12
Hampshire Hospitals NHS Foundation Trust, UK	6	6	12
CHU Lille, France	4	5	9
University of Chicago, USA	5	4	9
Whittington Health NHS Trust, UK	5	4	9
Jewish General Hospital, Montreal, Canada	4	4	8
Ghent University Hospital, Belgium	3	2	5
Bordeaux Pellegrin University Hospital, France	2	2	4
Princess Alexandra Hospital NHS Trust, UK	2	2	4
Radboud UMC, the Netherlands	2	2	4
Royal Free London NHS Foundation Trust, UK	2	2	4
University Hospital Bern, Switzerland	2	2	4
University Hospital Heidelberg, Germany	2	1	3
Hospices Civils de Lyon, Centre Hospitalier Lyon Sud, France	1	1	2
Weill Cornell Medicine New York-Presbyterian Hospital, USA	0	0	0
Hospices Civils de Lyon of the Hôpital Edouard Herriot, France	0	0	0
Total	**252**	**248**	**500**

5.2.2 Clinician experience in the PRECISION Trial

For TRUS biopsy, there were 38 operators who prior to the trial had performed a median of 750 TRUS biopsies each. For MRI-targeted biopsy, there were 33 operators who prior the trial had performed a median of 100 MRI-targeted biopsies. For MRI-reporting, 37 radiologists reported MRIs who had a median of 5 years of experience and reported a median of 300 MRI scans per year. For pathology reporting, there were 39 pathologists who had a median of 11 years of experience and reported a median of 230 prostate specimens per year (Table 5. 3).

Table 5. 3: Clinician experience in the PRECISION Trial as recorded at the start of the study

Adapted, with permission, from [49].

Clinician category	Total number in study	Experience of individual clinicians prior to starting study	
		Descriptor of experience	Median number, n (IQR)
TRUS biopsy operators	38	Number of TRUS biopsies previously performed	750 (300-1000)
		Number of TRUS biopsies performed per year	100 (50-190)
MRI-targeted biopsy operators	33	Number of MRI-targeted biopsies previously performed	100 (28-250)
		Number of MRI-targeted biopsies performed per year	60 (25-100)
Radiologists reporting MRI	37	Number of prostate MRIs reported per year	300 (200-500)
		Number of years of experience	5 (4.5-10)
Pathologists reporting prostate specimens	39	Number of patient's prostate specimens analyzed/year	230 (100-350)
		Number of years of experience	11 (8-20)

5.2.3 MRI Protocols for sites taking part in PRECISION

The MRI protocols adhered to minimum consensus guidelines for conduct of prostate MRI [46]. The key MRI parameters for sites, as per the START recommendations [63] are given in Table 5. 4. There were a range of different MRI manufacturers, field strengths and sequence protocols amongst sites.

Table 5. 4: MRI protocols for sites taking part in PRECISION

Reproduced, with permission, from [49].

Site	1	2	3	4	5	6	7	7	8
MRI manufacturer	Philips	Philips	GE	GE	Siemens	Philips	Siemens	Philips	Philips
MRI Model	Achieva	Ingenia	Discovery	Discovery	Skyra	Achieva	Avanto	Achieva	Ingenia
Field Strength	3T	3T	3T	3T	3T	1.5T	1.5T	3T	3T
Coils	PPA	PPA	PPA & ER	PPA	PPA	PPA & ER	PPA	PPA	PPA
Sequences used	T2, DWI, DCE	T2, DWI, DCE	T2, DWI, DCE	T2, DWI, DCE	T2, DWI, DCE	T2, DWI, DCE	T2, DWI, DCE	T2, DWI, DCE	T2, DWI, DCE
T2 sequence details									
Planes acquired	Axial, coronal, sagittal	Axial, coronal, sagittal	Axial, coronal, sagittal	Axial, coronal, sagittal	Axial, coronal, sagittal	Axial, coronal, sagittal	Axial, coronal	Axial, coronal	Axial, coronal, sagittal
Slice Thickness (axial)	3mm	3mm	3mm	3mm	3mm	3mm	3mm	3mm	3mm
Voxel size (axial)	0.389 x 0.389 x 3 mm	0.352 x 0.352 x 3 mm	0.435 x 0.435 x 3 mm	0.469 x 0.469 x 3 mm	0.521 x 0.521 x 3.3mm	0.312 x 0.312 x 3 mm	0.391 x 0.391 x 3.45 mm	0.375 x 0.375 x 3.3mm	0.37x0.37 x3mm
DCE sequence details									
Temporal resolution	6.91 s	10 s	5 s	6.5 s	7.4 s	9 s	11 s	11 s	3.2s
Model used for post-processing	DynaCAD	DynaCAD	genIQ	DynCAD	NR	NR	No	No	DynaCAD
Slice Thickness	4mm	3 mm	1.5 mm	3mm	3.6mm	3mm	3mm	3mm	3mm
Voxel size	0.75 x 0.75 x 4mm	1.3 x 1.3 x 3mm	1.02 x 1.02 x 1.5mm	0.859 x 0.859 x 3mm	1.35 x 1.35 x 3.6mm	0.625 x 0.625 x 3mm	0.677 x 0.677 x 3mm	0.938 x 0.938 x 3mm	1.02 x 1.02 x3mm

Site	1	2	3	4	5	6	7	7	8
Power Injector Gadolinium contrast Injection rate Flush given after Fat saturation (FS)/subtraction(SUB)	Yes Dotarem 3mls/s Yes Yes (FS)	Yes Gadovist 1ml/s Yes No	Yes Gadovist 3mls/s Yes Yes (FS)	Yes Dotarem 3mls/s Yes No	Yes Dotarem 2.5mls/s Yes No	Yes Gadobutrol 2mls/s Yes Yes (FS)	Yes Dotarem 3mls/s Yes Yes (FS)	Yes Dotarem 3mls/s Yes Yes (FS)	Yes Dotarem NR NR No
DWI sequence details									
B-values used	0,100,800, 2000	0,800,1600	0,500,1000, 3000	100,1000,1600	50,400,800, 1500, 3000	50,800,1600	0,150,500, 1000,1400	0,150,500, 1000,2000	0,50,1200
ADC threshold applied?	No	No	Yes	No	No	No	Yes	Yes	No
DWI combinations	Multi-b value, ADC & high b	Multi-b value, ADC & high b	Multi-b value, ADC & high b	Multi-b value, ADC & high b	Multi-b value, ADC & high b	Multi-b value, ADC & high b	Multi-b value, ADC & high b	Multi-b value, ADC & high b	Multi-b value & ADC
Slice Thickness	3mm	3mm	3mm	6mm	5mm	3mm	5mm	5mm	3mm
Voxel size	0.893 x 0.893 x 3mm	1.47 x 1.47 x 3mm	0.892 x 0.892 x 3 mm	1.02 x 1.02 x 6 mm	1.98 x 1.98 x 5.2 mm	1.25 x 1.25 x 3.3 mm	1.51 x 1.51 x 5 mm	0.98 x 0.982 x 5 mm	1.02x1.02 x3mm
Bowel Relaxant	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes

PPA = pelvic phased array, ER = endorectal, Res. = resolution, DCE = dynamic contrast enhanced, DWI = diffusion weighted imaging, s = second, NR = not reported

MRI protocols for sites taking part in PRECISION (continued…):

Site	9	10	11	12	13	14	15	16
MRI manufacturer	Philips	GE	Siemens	Philips	Philips	Philips	Siemens	Siemens
MRI Model	Achieva	Discovery	Aera	Ingenia	Ingenia	Achieva	Skyra	Trio
Field Strength	1.5T	3T	1.5T	1.5T	3T	1.5T	3T	3T
Coils	PPA	PPA	PPA	PPA	PPA & ER	PPA	PPA	PPA
Sequences used	T2, DWI, DCE	T2, DWI, DCE	T2, DWI, DCE	T2, DWI, DCE	T2, DWI, DCE	T2, DWI, DCE	T2, DWI, DCE	T2, DWI, DCE
T2 sequence details								
Planes acquired	Axial, coronal, sagittal	Axial, sagittal	Axial, coronal, sagittal	Axial, coronal, sagittal	Axial, coronal	Axial, coronal, sagittal	Axial, coronal, sagittal	Axial, coronal, sagittal
Slice Thickness (axial)	3mm	3mm	3mm	3mm	3 mm	3mm	3mm	3mm
Voxel size (axial)	0.417x0.417 x 3.3mm	0.371 x 0.371 x3.3mm	0.781x0.781 x 3.3mm	0.511x0.511 x3mm	0.45x0.45 x3mm	0.703x0.703 x3.3mm	0.625x0.625 x3mm	0.512 x0.512 x3mm
DCE sequence details								
Temporal resolution	18s	4-5s	17s	15s	7s	12 s	9.2s	9s
Model used for post-processing	NR	No	No	Tofts	No	No	No	No
Slice Thickness	1.5mm	4mm	3mm	3mm	1.5mm	3mm	3mm	3.6mm
Voxel size	0.488x0.488 x1.25mm	1.33x1.33 x1.5mm	0.875x0.875 x 3mm	0.625x.0.625 x3mm	0.994x0.994 x1.5mm	1.45x1.45 x3mm	1.25x1.25 x3.1mm	1.35x1.88 x3.6mm

Site	9	10	11	12	13	14	15	16
Power Injector Gadolinium contrast Injection rate Flush given after Fat saturation (FS)/subtraction(SUB)	No Dotarem 3mls/s Yes Yes (FS)	Yes Dotarem 3mls/s Yes Yes (FS)	Yes Dotarem 3mls/s Yes Yes (FS)	Yes Gadovist/Dotarem 2mls/s Yes No	Yes Multihance/Dotarem 2mls/s No Yes (FS)	Yes Gadovist 3mls/s Yes Yes (FS)	Yes Optimark/Omniscan 2.5mls/s Yes Yes (FS)	No Omniscan 3mls/sec Yes No
DWI sequence details B-values used ADC threshold applied? DWI combinations Slice Thickness Voxel size	 0,500,1000, 1400 No Multi-b value, ADC & high b 4.5mm 0.977x0.977 x 4.5 mm	 50,400,800 Yes Multi-b value & ADC 3mm 0.703x0.703 x 3.3mm	 0,150,500, 1000, 1400 Yes Multi-b value, ADC & high b 5mm 1.72x1.72x 5mm	 1,150,1000,2000 No Multi-b value & ADC 4mm 1.39x1.39x 4mm	 0,50,150,990,1500 No Multi-b value & ADC 3mm 1.12x1.12x3mm	 0,100,500, 1000,1400 Yes Multi-b value, ADC & high b 5mm 1.3x1.3 x5.5mm	 50 ,1400 No Multi-b value, ADC & high b 4mm 1.69x1.69x4mm	 50,400,800, 1200,1600 No Multi-b value, ADC & high b 3mm 1.62x2.14 x3mm
Bowel Relaxant	No	Yes	Yes	Yes	Yes	Yes	No	Yes

PPA = pelvic phased array, ER = endorectal, Res. = resolution, DCE = dynamic contrast enhanced, DWI = diffusion weighted imaging, s = second, NR = not reported

5.2.4 Baseline characteristics of population

The key baseline characteristics for patients in the two arms is give in Table 5. 5. The baseline characteristics were similar between arms with respect to age, PSA, family history of prostate cancer and abnormal digital rectal examination finding suspicious for malignancy.

Table 5. 5: Baseline Characteristics of population

Adapted, with permission, from [49].

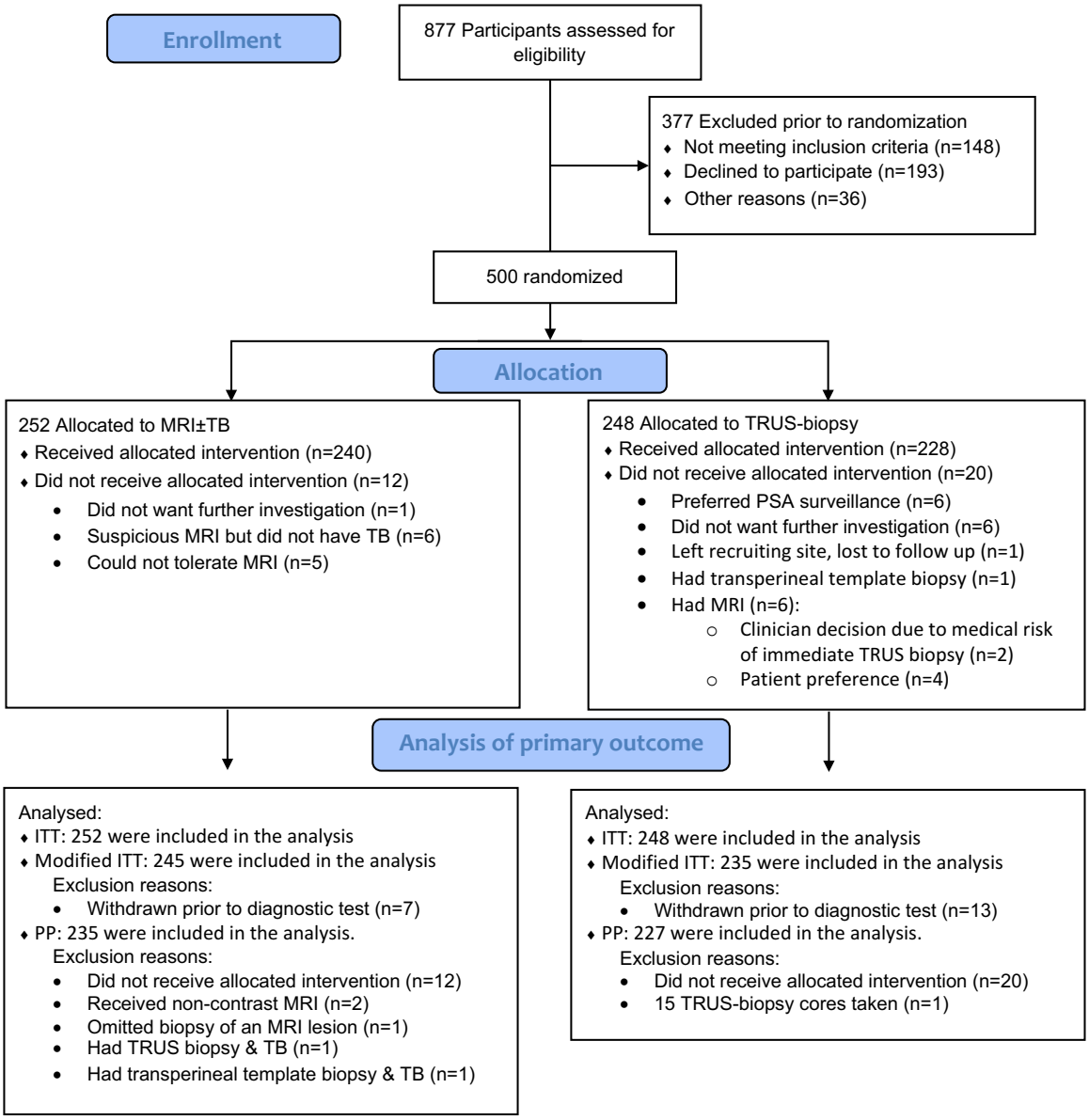
Characteristic	MRI±TB (N = 252)	TRUS biopsy (N = 248)
Age — yr		
Mean ± SD	64.4±7.5	64.5±8.0
PSA — ng/ml		
Median (IQR)	6.8 (5.2 to 9.4)	6.5 (5.2 to 8.7)
Family history of prostate cancer — no. (%)	48 (19.0)	40 (16.1)
Abnormal digital rectal examination — no. (%)	36 (14.3)	38 (15.3)

5.2.5 Patient flow

Eight hundred and seventy-seven patients were assessed for eligibility, of whom 377 were excluded prior to randomization, the majority of whom declined to participate (Figure 5. 2). In the MRI arm, of the 252 allocated to MRI ± targeted biopsy, 12 did not receive this, with 5/12 not being able to tolerate the MRI and 6/12 having a suspicious MRI but not undergoing MRI-targeted biopsy. In the TRUS biopsy arm, of the 248 allocated to TRUS biopsy, 20 did not receive this, with 12/20 men preferring PSA surveillance or not wanting further investigation. Another 6/20 men underwent MRI instead, 4 of whom decided they would prefer to undergo an MRI rather than a TRUS biopsy and 2 of whom the clinician decided that due to medical risk of immediate TRUS biopsy, an MRI would be preferable.

Figure 5. 2: Patient flow in the PRECISION trial

Adapted, with permission, from [49]. This contains the patient flow from enrolment to allocation to intervention to analysis of the primary outcome.



TB = Targeted biopsy, TRUS = Standard transrectal ultrasound guided prostate biopsy, PSA = Prostate specific antigen, ITT = Intention to treat analysis, PP = Per protocol analysis

5.2.6 Key MRI features of the patients in the MRI arm

The majority of patients in the MRI arm underwent MRI scanning with a 3 Tesla MRI machine (184/246, 75%) with the remaining undergoing MRI scanning with a 1.5T machine (62/246, 25%). Of those undergoing an MRI, 71/246 (29%) had an MRI that was not suspicious for significant cancer, that scored PIRADSv2 score 1

or 2. The remaining 175/246 (71%) men had at least one suspicious lesion with a PIRADSv2 score of 3, 4 or 5. The majority of men with a suspicious lesion had only 1 suspicious lesion (107/175, 61%). The highest PIRADSv2 score of 4 or 5 was seen in 124/175 (71%) men with a suspicious lesion. The median maximum MRI lesion diameter was 12mm (Table 5. 6).

Table 5. 6: Key MRI features in men in the MRI arm

Reproduced, with permission, from [49]. MRI±TB = MRI ± targeted biopsy.

Characteristic	MRI±TB (N = 246)*
Field strength of magnet — no. (%)	
1.5T	62 (25.2)
3.0T	184 (74.8)
MRI suspicion score — no. (%)	
1–2	71 (28.9)
3, 4 or 5	175 (71.1)
Suspicious lesions per patient — no. (%)†	
1 lesion	107 (61.1)
2 lesions	44 (25.1)
3 lesions	24 (13.7)
Highest MRI score for men with suspicious lesions‡ — no. (%)	
Score 3	51 (29.1)
Score 4	70 (40.0)
Score 5	54 (30.9)
MRI volume of prostate§ — mls	
Median (IQR)	46.0 (34.9 to 62.0)
Problems with MR quality — no. (%)	13 (5.3)
Median maximum lesion diameter (lesion-based)Δ — mm	
Median (IQR)	12 (8 to 15)
Median lesion volume (lesion-based)Δ — mls	0.6 (0.3 to 1.2)
Median (IQR)	

*Six of the patients in the MRI arm were protocol violators with no MRI data. Therefore, the number of patients is 246 unless indicated otherwise.
†Percentages are based on the 175 men with MRI suspicion score of 3, 4, or 5.
‡Each patient may have more than one suspicious lesion. The highest MRI score for each of the 175 patients with at least one suspicious lesion was included so that each patient contributed only one score.
§Prostate volume was unknown for one man and so the results are based on 245 men.
ΔCalculated using all lesions for each patient (lesion-based).

5.2.7 MRI-targeted biopsy technique

Of the recruiting sites, 18/23 sites carried out MRI-targeted biopsy via the transrectal route and 5/23 used the transperineal route. The registration approach used was exclusively software-assisted fusion in 14/23 sites, exclusively visual registration in 6/23 sites and used both techniques in 3/23 sites. Further details on the specific software system used, where applicable is given in Table 5. 7.

Table 5. 7: Approaches and techniques used for MRI-targeted biopsy

Reproduced, with permission, from [49].

Site	No. of men randomized to MRI±TB arm	Access route	Registration used	Name of software assisted system (where applicable)
1	37	Transrectal	Visual & Software-assisted	Philips UroNav
2	31	Transrectal	Visual & Software-assisted	UC-Care Medical Systems
3	31	Transrectal	Software-assisted	Koelis Urostation
4	27	Transrectal	Software-assisted	Philips UroNav
5	27	Transrectal	Software-assisted	Koelis Urostation
6	26	Transrectal	Software-assisted	BK Biojet
7	10	Transperineal	Visual	N/A
8	10	Transrectal	Software-assisted	Koelis Urostation
9	7	Transrectal	Visual	N/A
10	6	Transrectal	Software-assisted	Koelis Urostation
11	6	Transperineal	Visual	N/A
12	4	Transrectal	Software-assisted	Vnav Esaote
13	5	Transrectal	Visual & Software-assisted	Philips UroNav
14	5	Transperineal	Visual	N/A
15	4	Transrectal	Software-assisted	Koelis Urostation
16	3	Transrectal	Visual	N/A
17	2	Transrectal	Software-assisted	Philips EPIQ
18	2	Transperineal	Visual	N/A
19	2	Transrectal	Software-assisted	Toshiba Medical Aplio 500
20	2	Transrectal	Software-assisted	Philips UroNav
21	2	Transrectal	Software-assisted	Eigen Artemis
22	2	Transperineal	Software-assisted	Medcom BiopSee
23	1	Transrectal	Software-assisted	Koelis Urostation

5.2.8 Biopsy characteristics

Of the total number of patients allocated to the MRI arm, 71/252 (28%) avoided a biopsy. For the 169 men undergoing MRI-targeted biopsy a median of 4 cores were taken, compared to a median of 12 cores in the TRUS biopsy arm. The median length of the procedure (from when the transrectal probe was inserted to when it was removed) was 15 minutes in the MRI-targeted biopsy arm compared to 10 minutes in the TRUS biopsy arm. The majority of patients in both arms underwent biopsy under local anaesthetic (114/169, 68% for MRI-targeted biopsy versus 196/228, 86% for TRUS biopsy).

Table 5. 8: Biopsy details of men undergoing MRI-targeted biopsy and TRUS biopsy

Reproduced, with permission, from [49].

	MRI-TB (N = 169)	TRUS biopsy (N = 228)
TRUS volume of prostate — mls		
Median (IQR)	40.5 (32.0–54.8)	43.7 (33.3–60.0)
Number of biopsies taken		
Median (IQR)	4 (3 to 7)	12 (12 to 12)
Length of procedure — mins*		
Median (IQR)	15 (10 to 25)	10 (9 to 15)
Anaesthetic — no. (%)		
Local	114 (67.5)	196 (86.0)
Sedation/general anaesthetic/spinal	55 (32.5)	32 (14.0)

*Length of procedure based on time from when TRUS probe inserted prior to procedure to when TRUS probe removed at end of procedure. MRI-TB = MRI-targeted biopsy.

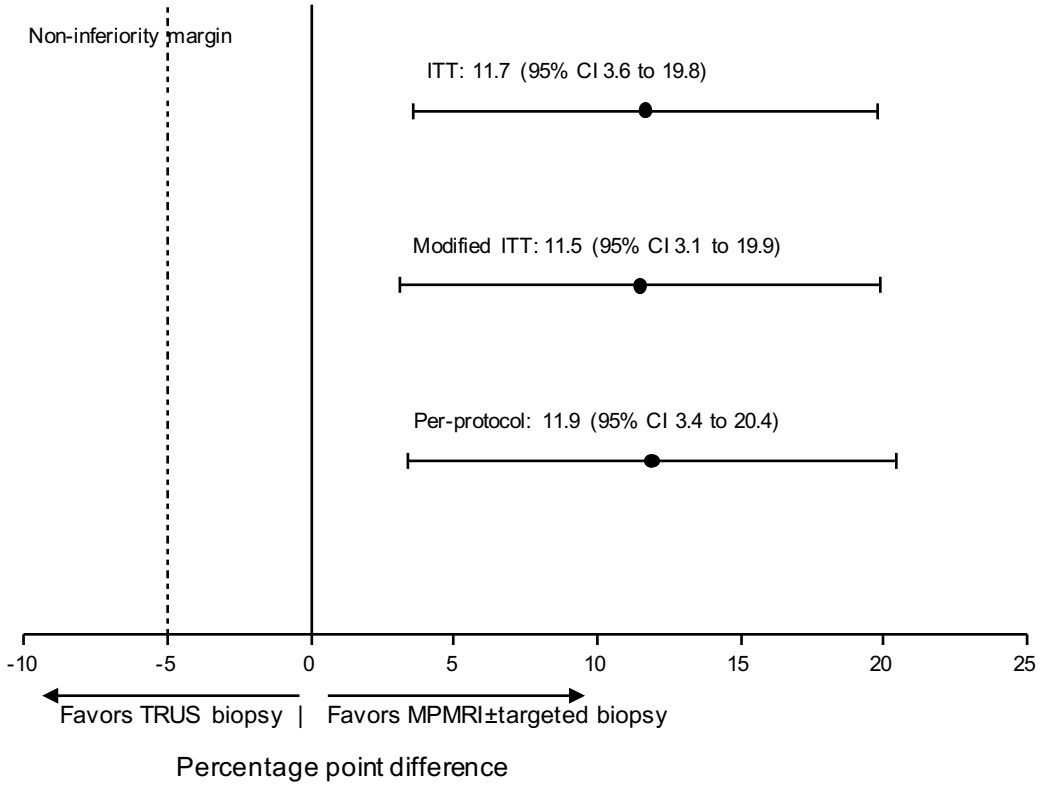
5.2.9 Primary outcome: clinically significant cancer detection

A greater proportion of men in the MRI ± targeted biopsy arm (95/252, 38%) were diagnosed with clinically significant cancer (Gleason 3+4 or greater) than in the TRUS biopsy arm (64/248, 26%), adjusted difference, 12%, 95% CI 4-20, p = 0.005. The lower bound of the 95% CI was greater than the non-inferiority margin of clinical unimportance of -5%, therefore MRI ± targeted biopsy was non-inferior to TRUS biopsy on the intention to treat analysis (Figure 5. 3). In addition, as the

lower bound of the 95% CI was greater than the null, this indicated that MRI ± targeted biopsy was superior to TRUS biopsy in the detection of clinically significant cancer. In the modified intention to treat analysis, when excluding patients who withdrew prior to any fully completed diagnostic test, the results were consistent, with an adjusted difference of 12%, 95% CI 3-20%. In the per protocol analysis, when excluding patients who did not follow the protocol, the results were consistent, with an adjusted difference of 12%, 95% CI 3-20%. Details of reasons for exclusion are given in Figure 5. 2.

Figure 5. 3: Graphical depiction of the analyses of the primary outcome

Adapted, with permission, from [49]. ITT = Intention to treat analysis. The non-inferiority margin was set a priori to -5% and represented the lowest value that the lower bound of the 95% CI for the difference in clinically significant cancer detection between arms could reach to allow one to declare that MRI-targeted biopsy was non-inferior to TRUS biopsy. As the lower bound of the 95% CI for ITT, modified ITT and per protocol analyses was above the null (0), superiority of MRI-targeted biopsy over TRUS biopsy could be claimed.



A detailed breakdown of cancer detection is given in Table 5. 9.

Table 5. 9: Detailed cancer detection comparison between MRI ± targeted biopsy and TRUS biopsy

Adapted, with permission, from [49].

	MRI±TB (n = 252)	TRUS biopsy (n = 248)	Difference	P value
Biopsy outcome; no. (%)				
Negative MRI, avoided biopsy	71 (28.2)	0		
Benign tissue	52 (20.6)	98 (39.5)		
ASAP	0	5 (2.0)		
HGPIN	4 (1.6)	10 (4.0)		
Gleason 3+3	23 (9.1)	55 (22.2)		
Gleason 3+4	52 (20.6)	35 (14.1)		
Gleason 3+5	2 (0.8)	1 (0.4)		
Gleason 4+3	18 (7.1)	19 (7.7)		
Gleason 4+4	13 (5.2)	6 (2.4)		
Gleason 4+5	7 (2.8)	2 (0.8)		
Gleason 5+5	3 (1.2)	1 (0.4)		
No biopsy†	4 (1.6)	3 (1.2)		
Withdrawn‡	3 (1.2)	13 (5.2)		
Proportion of men with clinically significant cancer (≥Gleason 3+4) – no./total number (%)				
ITT	95/252 (37.7)	64/248 (25.8)	11.7 (3.6-19.8)	0.005
Modified ITT	95/245 (38.8)	64/235 (27.2)	11.5 (3.1-19.9)	0.007
Per-protocol	92/235 (39.1)	62/227 (27.3)	11.9 (3.4-20.4)	0.007
Proportion of men with clinically insignificant cancer (Gleason 3+3)- no./total number (%)	23/252 (9.1)	55/248 (22.2)	-13.1 (-19.3- -6.8)	<0.001
Maximum cancer core length, mm, mean±SD	7.8±4.1	6.5±4.5	1.04 (-0.01–2.10)	0.053
Proportion of cores positive for cancer – no./total number (%)	422/967 (43.6%)	515/2788 (18.5%)		
Proportion of men who did not have biopsy no./total number (%)	78/252 (31.0%)	16/248 (6.5%)		

†For those in the MRI±TB arm, MRI identified at least one suspicious area with a score of 3 or greater but targeted biopsy was not performed. For those in the TRUS-biopsy arm, patient refused TRUS-biopsy and had an MRI. MRI showed no suspicious area and patient avoided biopsy.

‡These patients did not complete any diagnostic test.

The main contribution for the increase in clinically significant cancer detection by MRI ± targeted biopsy was the increased detection of Gleason 3+4 cancer, with MRI ± targeted biopsy detecting 52/252 (21%) of men with this compared to TRUS biopsy detecting 35/248 (14%). MRI ± targeted biopsy also detected 6% [95% CI 1-10%] more Gleason sum 8-10 cancers than TRUS biopsy.

5.2.10 Clinically insignificant cancer detection

Fewer men in the MRI ± targeted biopsy group (23/252, 9%) had clinically insignificant cancer (Gleason 3+3) diagnosed than in the TRUS biopsy arm (55/248, 22%), adjusted difference 13%, 95% CI 7-19%, $p < 0.001$.

5.2.11 Proportion of cores positive for cancer

In the MRI ± targeted biopsy arm, a greater proportion of biopsy cores taken had cancer in (422/967, 44%) when compared to the TRUS biopsy arm (515/2788, 19%).

5.2.12 Maximum cancer core length

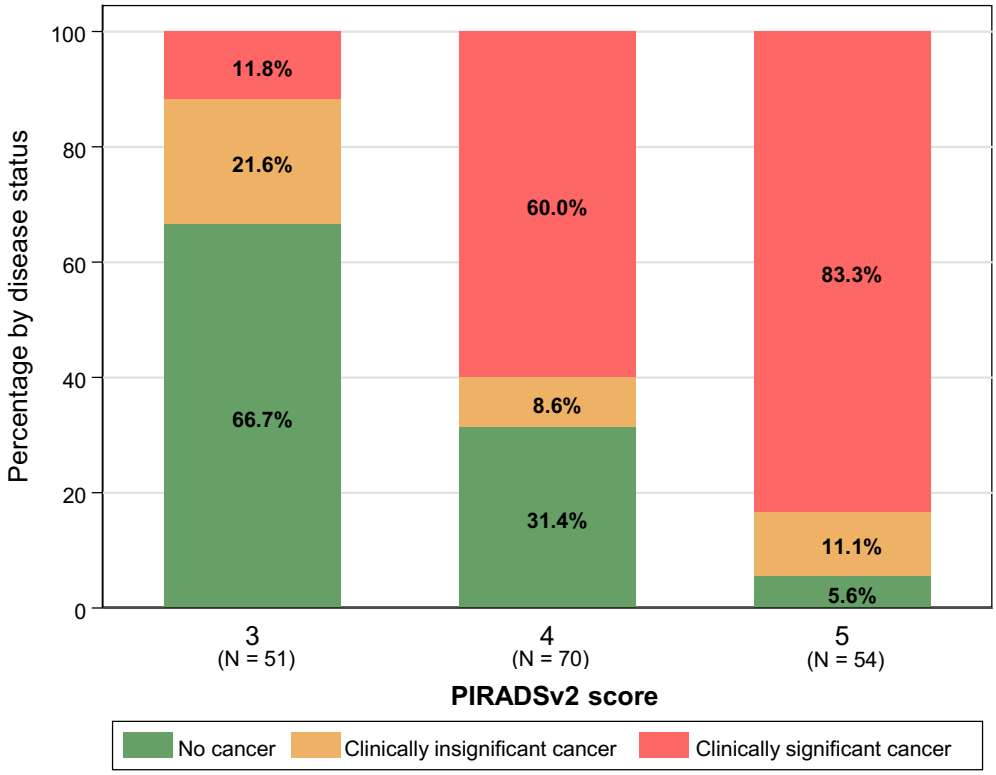
In biopsies with cancer in, mean maximum cancer core length in the MRI ± targeted biopsy group was 7.8mm compared to 6.5mm in the TRUS biopsy group, difference 1.04mm, 95% CI -0.01-2.10), $p = 0.053$.

5.2.13 Cancer detection by PIRADSv2 score

Clinically significant cancer was detected in 83% of men with PIRADSv2 score of 5, 60% of men with PIRADSv2 score of 4 and 12% of men with PIRADSv2 score of 3. No cancer was detected in 67% of men with PIRADSv2 score of 3, 31% of men with a PIRADSv2 score of 4 and 6% of men with a PIRADSv2 score of 5 (Figure 5. 4).

Figure 5. 4: Graphical depiction of the cancer status of men given by PIRADSv2 score

Adapted, with permission, from [49].



5.2.14 Health-related quality of life

For the MRI ± targeted biopsy group, the mean baseline EQ-5D quality of life descriptive score was 0.909, at 24 hours after intervention was 0.907 and at 30 days after intervention was 0.917 (higher scores indicate better quality of life, on a scale where 0 is the worst quality of life and 1 is the best quality of life). For TRUS biopsy, the mean baseline EQ-5D quality of life descriptive score was 0.907, at 24 hours after intervention was 0.894 and at 30 days was 0.921 (Table 5. 10). The mean difference in descriptive scores between the MRI ± targeted biopsy group and TRUS biopsy group was not significant at 24 hours (difference 0.006, 95% CI -0.017-0.029, p = 0.61) or at 30 days (difference -0.004, 95% CI -0.028-0.02, p = 0.72). There was also no difference in the EQ-5D quality of life visual analogue scores between MRI ± targeted biopsy and TRUS biopsy arms at 24 hours post intervention or at 30 days post intervention.

Table 5. 10: Health-related quality of life at baseline, 24 hours after intervention and 30 days after intervention

Reproduced, with permission, from [49]. Higher EQ-5D scores indicate better quality of life. For the comparison of the two arms, mean differences (value in the MRI±TB arm minus value in the TRUS biopsy arm) were estimated using repeated measures mixed models with adjustment for baseline levels. There was no difference in health-related quality of life at 24 hours or 30 days post intervention.

Variable	Baseline		24 hours		Mean difference (95% CI)	P value	30 days		Mean difference (95% CI)	P value
	MRI±TB* (N = 245)	TRUS biopsy (N = 238)	MRI±TB* (N = 215)	TRUS biopsy (N = 200)			MRI±TB* (N = 200)	TRUS biopsy (N = 192)		
EQ-5D descriptive score	0.909±0.137	0.907±0.123	0.907±0.126	0.894±0.159	0.006 (-0.017 to 0.029)	0.61	0.917±0.124	0.921±0.126	-0.004 (-0.028 to 0.020)	0.72
EQ-5D VAS score	85.6±11.8	85.5±10.2	84.8±10.8	84.2±11.3	0.61 (-0.95 to 2.18)	0.44	84.6±11.9	85.7±10.3	-0.27 (-1.88 to 1.33)	0.74

Plus–minus values are means ±SD. MRI±TB = MRI±targeted biopsy, TRUS = Transrectal ultrasound guided.
*If the patient only underwent MRI and did not undergo biopsy, the 24-hour and 30-day post intervention questionnaires refer to the post MRI questionnaires. If the patient underwent MRI and targeted biopsy, the questionnaires refer to the post-biopsy questionnaires. Scores from the domains of the European Quality of Life 5 Dimensions 5-Level (EQ-5D-5L) Questionnaire were converted to EQ-5D descriptive scores using the value set for the United Kingdom.

5.2.15 Patient-reported complications post biopsy

Immediate post intervention pain was similar between the MRI ± targeted biopsy group (median analogue score 1, scored from 0-10, where higher scores indicated worse pain) and the TRUS biopsy group (median analogue score 2). At 30-days post intervention, a lower proportion of men in the MRI ± targeted biopsy compared to the TRUS biopsy group reported experiencing blood in the urine (14% vs 22%, respectively), blood in the semen (32% vs 60%, respectively), blood in the back passage (14% vs 22%, respectively), erectile dysfunction (11% vs 16%, respectively) and pain at the site of the procedure (13% vs 23%, respectively). A similar proportion of patients reported fever, acute urinary retention, urinary incontinence and urinary tract infection (Table 5. 11). Of note, 1% of patients in the MRI ± targeted biopsy said a repeat procedure would be a major problem, but 5% of patients in the TRUS biopsy said a repeat procedure would be a major problem.

Table 5. 11: Patient-reported complications

Adapted, with permission, from [49]. 30-day complications given as number of patients,

	MRI±TB*	**TRUS biopsy**
Immediate post-intervention complications†	**N = 224**	**N = 222**
Discomfort, Median (IQR)	2 (0–4)	3 (2–5)
Pain, Median (IQR)	1 (0–3)	2 (1–4)
30-day post-intervention complications	**N = 212, (%)**	**N = 206, (%)**
Pain at site of procedure	27 (12.7)	48 (23.3)
Fever	9 (4.2)	9 (4.4)
Blood in the urine	64 (30.2)	129 (62.6)
Blood in the semen	68 (32.1)	123 (59.7)
Blood in the stools or from the back passage	30 (14.2)	45 (21.8)
Acute urinary retention	3 (1.4)	2 (1.0)
Erectile dysfunction	23 (10.8)	32 (15.5)
Urinary incontinence	13 (6.1)	10 (4.9)
Urinary tract infection	5 (2.4)	2 (1.0)
Men for whom another procedure would be a major problem	2 (0.9)	10 (4.9)

*If the patient only underwent MRI and did not undergo biopsy, the immediate intervention questionnaire refers to the post MRI questionnaire. If the patient underwent MRI and biopsy, the questionnaire refers to the post-biopsy questionnaire. 174 patients underwent a prostate biopsy in the MRI arm.

5.2.16 Investigator-reported adverse events

Investigator-reported adverse events and serious adverse events were low in frequency in both arms. There were serious adverse events in 2% of patients in each arm, MRI ± targeted biopsy (4/252) and TRUS biopsy (5/248). One man experienced sepsis in the MRI ± targeted biopsy group (1/252, 0.4%) and 4 men experienced sepsis in the TRUS biopsy group (4/248, 1.6%). Unrelated to the trial intervention, one man experienced a pulmonary embolism in the MRI ± targeted biopsy group and one man died in the MRI ± targeted biopsy group from a pulmonary metastasis of pre-existing squamous cell carcinoma. Unrelated to the trial intervention, 1 man in the TRUS biopsy group experienced a myocardial infarction (Table 5. 12).

Table 5. 12: A table summarizing investigator-reported adverse events

Reproduced, with permission, from [49].

Characteristic	MRI±TB (N = 252) N (%)	TRUS biopsy (N = 248) N (%)
Number of adverse events		
Serious adverse events	4 (1.6)	5 (2.0)
Adverse events	2 (0.8)	3 (1.2)
Adverse events related to intervention		
Sepsis	1 (0.4)	4 (1.6)
Haematuria	0 (0)	1 (0.4)
Prostatitis	3 (1.2)	0 (0)
Adverse events unrelated to intervention		
Fatigue	0 (0)	1 (0.4)
Runny nose and cough	0 (0)	1 (0.4)
Myocardial infarction	0 (0)	1 (0.4)
Pulmonary embolism	1 (0.4)	0 (0)
Death (secondary to pulmonary metastasis of known squamous cell carcinoma)	1 (0.4)	0 (0)

5.2.17 Treatment decision following the protocol investigation results

Once the results of the protocol test were available and discussed with the patient, in the MRI ± targeted biopsy arm, 7/252 (3%) men had further diagnostic tests ordered compared to 39/248 (16%) in the TRUS biopsy arm. The main subsequent test being ordered in the TRUS biopsy arm after the protocol test was an MRI of the prostate, a decision in 38/39 cases of which was led by the treating clinician. In the MRI ± targeted biopsy arm, 3/7 men had further MRIs, primarily due to inadequate quality of the first MRI and 4 men had a further immediately biopsy.

A similar proportion of patients in each arm were discharged from the treating clinician's care after the protocol test results (5% vs 6% for MRI ± targeted biopsy and TRUS biopsy, respectively). Twelve percent of patients in both arms entered an active surveillance program. In the MRI ± targeted biopsy arm, 70/252 (27%) of men underwent radical treatment for localised prostate cancer compared to 60/248 (24%) of men in the TRUS biopsy arm. A slightly higher proportion of men underwent radical prostatectomy in the MRI ± targeted biopsy arm compared to the TRUS biopsy arm (14% versus 12%, respectively) and a slightly higher proportion of men underwent radical radiotherapy in the MRI ± targeted biopsy compared to the TRUS biopsy arm (14% versus 11%, respectively).

In terms of subsequent tests arranged by the treating clinician for the purpose of staging diagnosed prostate cancer, more men had MRIs of the pelvis for staging in the TRUS biopsy arm (39/248, 16%) than in the MRI ± targeted biopsy arm (2/252, 1%). A bone scan was carried out more commonly for men in the MRI ± targeted biopsy arm than the TRUS biopsy arm (52/252, 21% vs 37/248, 15%) (Table 5. 13).

Table 5. 13: Treatment decisions made for men in the study

Reproduced, with permission, from [49].

Treatment decision	MRI±TB (N =252) N (%)	TRUS biopsy (N = 248) N (%)
Discharge patient, no treatment or follow up required	13 (5.2)	15 (6.0)
PSA monitoring	104 (41.3)	74 (29.8)
Active Surveillance	29 (11.5)	29 (11.7)
Radical treatment	70 (27.0)	60 (24.2)
Radical prostatectomy	34 (13.5)	30 (12.1)
Radiotherapy ± neoadjuvant hormone therapy	35 (13.9)	26 (10.5)
Brachytherapy	1 (0.4)	4 (1.6)
Focal therapy	1 (0.4)	0 (0)
Hormone therapy ± chemotherapy	2 (0.8)	2 (0.8)
Watchful waiting	1 (0.4)	2 (0.8)
Other treatment decisions	11 (4.4)	7 (2.8)
Unknown	14 (5.6)	20 (8.1)
Further diagnostic tests ordered from treatment decision visit	7 (2.7)	39 (15.7)
MRI for diagnosis	3 (1.2)	38 (15.3)
Patient choice	0	1
Clinician choice	3	37
Immediate further prostate biopsies	4 (1.6)	1 (0.4)
Patient choice	1	0
Clinician choice	3	1
Further staging tests*		
MRI for staging	2 (0.8)	39 (15.7)
Bone scan	52 (20.6)	37 (14.9)
CT	33 (13.1)	31(12.5)
PET-CT	0 (0)	1 (0.4)
PET-MRI	0 (0)	1 (0.4)

*A patient can have more than one type of staging scan. Therefore, the percentages were calculated by dividing the number of patients who received the scan by the total number in the arm.

5.2.18 Outcomes of men undergoing further diagnostic tests following the protocol test

Of the 3 men who had repeat MRIs in the MRI ± targeted biopsy arm, none of the repeat MRIs identified suspicious areas. Of the 38 men in the TRUS biopsy arm who had further MRIs, 18/38 (47%) had suspicious areas on MRI and 7/38 (18%) had MRIs whose interpretation was affected by post-biopsy haemorrhage.

For the 4 men who had further biopsy in the MRI ± targeted biopsy arm, none had cancer diagnosed. For the 9 men who had further biopsies in the TRUS biopsy arm, 4 had cancer diagnosed, with 3 having clinically significant cancer diagnosed, with median maximum cancer core length of 6.5mm (Table 5. 14).

Table 5. 14: A table summarizing outcomes of men undergoing further diagnostic tests after the protocol test

Adapted, with permission, from [49].

Characteristic	MRI±TB	TRUS biopsy
Further MPMRI following treatment decision — no.	3	38
MPMRI identified suspicious areas scoring 3 or greater — no. (%)		
Yes	0 (0)	18 (47.4)
No	3 (100)	20 (52.6)
MPMRI with post-biopsy artefact — no. (%)	0 (0)	7 (18.4)
MPMRI led to further biopsy — no.	0 (0)	8
Further biopsies following treatment decision — no.(%)	4	9
Transperineal template biopsy	0 (0)	1 (11.1)
10-12 core transrectal biopsy	3 (75.0)	0 (0)
MRI-targeted prostate biopsy	1 (25.0)	8 (88.9)
Overall Gleason grade from further biopsy — no. (%)		
Benign	3 (75.0)	5 (55.6)
ASAP	1 (25.0)	0 (0)
3+3	0 (0)	1 (11.1)
3+4	0 (0)	3 (33.3)
Maximum cancer core length[†] — mm		
Median (IQR)	NA	6.5 (4.0 to 8.5)

NA = not applicable

[†]Data were available for 4 of the 9 patients in the TRUS biopsy arm

5.2.19 Radical prostatectomy Gleason grade concordance with biopsy

In men undergoing radical prostatectomy in each arm, the Gleason grade of the biopsy was compared to the Gleason grade of the radical prostatectomy specimen. In the MRI ± targeted biopsy arm 19/30 (63%) of those undergoing radical prostatectomy had concordant biopsy to prostatectomy specimens, 5/30 (17%) were upgraded and 6/30 (20%) were downgraded. In the TRUS biopsy arm 19/27 (70%) specimens were concordant, 4/27 (15%) specimens were upgraded and 4/27 (15%) were downgraded. There was missing data for 4 men

in the MRI ± targeted biopsy arm and 3 men in the TRUS biopsy arm. Men with missing data were those with a treatment decision for radical prostatectomy but who had not undergone the procedure at the time of the study closure.

5.2.20 Quality control for MRI reporting

In order to check the quality of reporting of MRI within the trial, 25% of the MRIs from each site were chosen at random and reported centrally by the coordinating site by two uro-radiologists in consensus, blinded to the original MRI report and pathology outcomes. The central radiologists had 5 and 15 years of experience, reporting approximately 1000 prostate MRI scans per year each.

Based on an MRI score of suspicion of a lesion being a 3, 4 or 5 as the scores that would trigger a biopsy of an MRI lesion, a measure of agreement by concordant biopsy decision was evaluated (Table 5. 15). In 50/64 (78%) of cases, there was agreement by concordant biopsy decision between the local site and central quality control radiologists.

Table 5. 15: Agreement in concordant biopsy decision by PIRADSv2 score between local site radiologist and central quality control interpretation

Adapted, with permission, from [49].

		PIRADsv2 score for MRI as reported centrally					
		1	2	3	4	5	TOTAL
PIRADSv2 score for MRI reported by local site radiologist	1	10	-	1	4	-	15
	2	-	5	-	1	-	6
	3	1	6	2	1	1	11
	4	1	-	-	8	5	14
	5	-	-	1	2	15	18
	TOTAL	12	11	4	16	21	64

Key:

Concordant scores, where management decision to perform biopsy would not have changed

Discordant scores, where management decision to perform biopsy would have changed

5.2.21 Quality control for pathology reporting

In order to check the quality of reporting of pathology within the trial, 15% of the biopsy slides from each site were chosen at random and reported centrally by the coordinating site by one of 4 pathologists at the coordinating centre. The quality control pathologists were blinded to the original pathology report. The central pathologists had 23, 14, 8 and 3 years of experience, reporting approximately 100, 100, 100 and 250 prostate specimens per year, respectively.

Agreement with local site pathologists was present in 53/60 (88%) of cases. In 3/60 (5%) cases, the local site pathology was upgraded by the central quality

control pathologist; in 4/60 (7%) cases, the local site pathology was downgraded by the central quality control pathology (Table 5. 16).

Table 5. 16: Table of agreement between local site and central pathologist report for Gleason grading of cancer identified

Adapted, with permission, from [49].

		Overall Gleason grade by central pathology review							
		Benign	Gleason 3+3	Gleason 3+4	Gleason 3+5	Gleason 4+3	Gleason 4+4	Gleason 4+5	TOTAL
Overall Gleason grade as reported by local site pathologist	Benign	26	1	1	-	-	-	-	28
	Gleason 3+3	-	8	1	-	-	-	-	9
	Gleason 3+4	-	1	13	-	-	-	-	14
	Gleason 3+5	-	-	-	1	-	-	-	1
	Gleason 4+3	-	-	1	-	1	-	-	2
	Gleason 4+4	-	-	-	-	1	1	-	2
	Gleason 4+5	-	-	-	-	-	-	3	3
	Gleason 5+4	-	-	-	-	-	-	1	1
	TOTAL	26	10	16	1	2	1	4	60

5.2.22 Cost effectiveness resource use sources and unit costs considered

For the cost-effectiveness analysis, the NHS Reference Costs were the basis of the resource use costs [79], with supplementation from the National Collaborating Centre for Cancer [80] and the Unit Costs of Health and Social Care [81]. Short-run cost-effectiveness was calculated from a health system perspective including costs of the diagnostic tests, staging tests and health care contacts within 30 days. Inflation of costs were used to standardise costs to 2016 prices where 2016 prices were not already given.

The considered costs, lower quartiles (LQ), upper quartiles (UQ), sources and rationale for derivation of costs is given in Table 5. 17.

Table 5. 17: Cost-effectiveness resource use sources and unit costs considered

Resource	Source	Unit Cost (£)
TRUS biopsy, outpatient	NHS Reference Costs 2015-2016 Outpatient LB76Z Transrectal ultrasound guided biopsy of prostate: £254 (LQ £161- UQ £295). National Collaborating Centre for Cancer, commissioned by National Institute for Clinical Excellence 2014: Pathology costs inflated from 2014 to 2016 using the hospital & community health services (HCHS) index: £115.31	369.31
TRUS biopsy, day case	NHS Reference Costs 2015-2016 Day case LB76Z Transrectal ultrasound guided biopsy of prostate: £544 (LQ £349 – UQ £720). National Collaborating Centre for Cancer, commissioned by National Institute for Clinical Excellence 2014: Pathology costs inflated from 2014 to 2016 using the hospital & community health services (HCHS) index: £115.31	659.31
Diagnostic multi-parametric MRI	NHS Reference Costs 2015-2016: Outpatient RD03Z Magnetic Resonance Imaging Scan (1 area, pre and post contrast)	205.00

Resource	Source	Unit Cost (£)
MRI-TB, transrectal visually registered, outpatient	NHS Reference Costs 2015-2016: Outpatient LB76Z Transrectal ultrasound guided biopsy of prostate: £254 (LQ £161- UQ £295). National Collaborating Centre for Cancer, commissioned by National Institute for Clinical Excellence 2014: Pathology costs inflated from 2014 to 2016 using the hospital & community health services (HCHS) index: £115.31	369.31
MRI-TB, transperineal visually registered, outpatient	NHS Reference Costs 2015-2016: Outpatient, LB77Z Transperineal Template Biopsy of Prostate: £275 (LQ £107- UQ £269). National Collaborating Centre for Cancer, commissioned by National Institute for Clinical Excellence 2014: Pathology costs inflated from 2014 to 2016 using the hospital & community health services (HCHS) index: £115.31	390.31
MRI-TB, transrectal visually registered, day case	NHS Reference Costs 2015-2016: Day case LB76Z Transrectal ultrasound guided biopsy of prostate: £544 (LQ £349 – UQ £720). National Collaborating Centre for Cancer, commissioned by National Institute for Clinical Excellence 2014: Pathology costs inflated from 2014 to 2016 using the hospital & community health services (HCHS) index: £115.31	659.31
MRI-TB, transperineal visually registered, day case	NHS Reference Costs 2015-2016: Outpatient, LB77Z Transperineal Template Biopsy of Prostate: £1360 (LQ £1043 –UQ £1520). Decision to use lower quartile price (£1043) as the NHS reference cost provided accounts primarily for full transperineal template prostate biopsies (approximately 20-30 cores per patient) whereas in PRECISION, the median number of targeted cores taken was 4 per patient. National Collaborating Centre for Cancer, commissioned by National Institute for Clinical Excellence 2014: Pathology costs inflated from 2014 to 2016 using the hospital & community health services (HCHS) index: £115.31	1158.31

Resource	Source	Unit Cost (£)
MRI-TB, transrectal software-assisted, outpatient	NHS Reference Costs 2015-2016: Outpatient LB76Z Transrectal ultrasound guided biopsy of prostate: £254 (LQ £161- UQ £295). National Collaborating Centre for Cancer, commissioned by National Institute for Clinical Excellence 2014: Pathology costs inflated from 2014 to 2016 using the hospital & community health services (HCHS) index: £115.31 National Collaborating Centre for Cancer, commissioned by National Institute for Clinical Excellence 2014: "Software-assisted additional cost component associated with the extra capital equipment and time required to perform the procedure. Capital equipment costs were estimated by first calculating annuitized costs using an initial upfront capital cost of £100,000, an expected useful lifespan of 7 years and a discount rate of 3.5% per year. Cost per minute estimates were then calculated by following the methodology used previously. The cost per minute was then multiplied by usage time estimates (15 minutes registration after the mpMRI scan is done). In addition, this registration is assumed to be performed by two radiographers and so this cost is also added". Costs inflated from 2014 to 2016 using the HCHS index: £27.47	396.78
MRI-TB, transperineal software-assisted, outpatient	NHS Reference Costs 2015-2016: Outpatient, LB77Z Transperineal Template Biopsy of Prostate: £275 (LQ £107- UQ £269). National Collaborating Centre for Cancer, commissioned by National Institute for Clinical Excellence 2014: Pathology costs inflated from 2014 to 2016 using the hospital & community health services (HCHS) index: £115.31 National Collaborating Centre for Cancer, commissioned by National Institute for Clinical Excellence 2014: "Software-assisted additional cost component associated with the extra capital equipment and time required to perform the procedure. Capital equipment costs were estimated by first calculating annuitized costs using an initial upfront capital cost of £100,000, an expected useful lifespan of 7 years and a discount rate of 3.5% per year. Cost per minute estimates were then calculated by following the methodology used previously. The cost per minute was then multiplied by usage time estimates (15 minutes registration after the mpMRI scan is done). In addition, this registration is assumed to be performed by two radiographers and so this cost is also added". Costs inflated from 2014 to 2016 using the HCHS index: £27.47	417.78

Resource	Source	Unit Cost (£)
MRI-TB, transrectal software-assisted, day case	NHS Reference Costs 2015-2016: Day case LB76Z Transrectal ultrasound guided biopsy of prostate: £544 (LQ £349 – UQ £720). National Collaborating Centre for Cancer, commissioned by National Institute for Clinical Excellence 2014: Pathology costs inflated from 2014 to 2016 using the hospital & community health services (HCHS) index: £115.31 National Collaborating Centre for Cancer, commissioned by National Institute for Clinical Excellence 2014: "Software-assisted additional cost component. Capital equipment costs were estimated by first calculating annuitized costs using an initial upfront capital cost of £100,000, an expected useful lifespan of 7 years and a discount rate of 3.5% per year. Cost per minute estimates were then calculated by following the methodology used previously. The cost per minute was then multiplied by usage time estimates (15 minutes registration after the mpMRI scan is done). In addition, this registration is assumed to be performed by two radiographers and so this cost is also added". Costs inflated from 2014 - 2016 using the HCHS index: £27.47	686.78
MRI-TB, transperineal software-assisted, day case	NHS Reference Costs 2015-2016: Day case LB77Z Transperineal Template Biopsy of Prostate: £1360 (LQ £1043 –UQ £1520). Used lower quartile price (£1043) as the NHS reference cost provided accounts for full transperineal template prostate biopsies (approximately 20-30 cores per patient) whereas in PRECISION, the median number of targeted cores taken was 4 per patient. National Collaborating Centre for Cancer, commissioned by National Institute for Clinical Excellence 2014: Pathology costs inflated from 2014 to 2016 using the hospital & community health services (HCHS) index: £115.31 National Collaborating Centre for Cancer, commissioned by National Institute for Clinical Excellence 2014: "Software-assisted additional cost component associated with the extra capital equipment and time required to perform the procedure. Capital equipment costs were estimated by first calculating annuitized costs using an initial upfront capital cost of £100,000, an expected useful lifespan of 7 years and a discount rate of 3.5% per year. Cost per minute estimates were then calculated by following the methodology used previously. The cost per minute was then multiplied by usage time estimates (15 minutes registration after the mpMRI scan is done). In addition, this registration is assumed to be performed by two radiographers and so this cost is also added". Costs inflated from 2014 - 2016 using the HCHS index: £27.47	1185.78

Resource	Source	Unit Cost (£)
Transperineal template prostate biopsy	NHS Reference Costs 2015-2016: Day case LB77Z Transperineal Template Biopsy of Prostate: £1360 (LQ £1043 –UQ £1520).	1360.00
Staging multi-parametric MRI scan, pelvis	NHS Reference Costs 2015-2016: Outpatient RD03Z Magnetic Resonance Imaging Scan (1 area, pre and post contrast)	205.00
Staging CT scan, pelvis	NHS Reference Costs 2015-2016: OUTPATIENT, UROLOGY RD22Z Computerised Tomography Scan of one area, with pre and post contrast: £119 (LQ £95- UQ £138)	119.00
Staging Bone scan	NHS Reference Costs 2015-2016: OUTPATIENT, UROLOGY RN15A Nuclear Bone Scan of two or three phases, 19 years and over	242.00
Staging PET-CT scan	NHS Reference Costs 2015-2016: OUTPATIENT, UROLOGY RN02A Positron Emission Tomography with Computed Tomography (PET-CT) of two or three areas, 19 years and over	436.00
Staging PET-MRI scan	NHS Reference Costs 2015-2016: OUTPATIENT UROLOGY RN34A Other Specified Diagnostic Imaging of Other Sites, 19 years and over	484.00
Emergency department attendance	NHS Reference Costs 2015-2016: Service code 180, taking into consideration both consultant led and non-consultant led care	146.86
Hospital admission	NHS Reference Costs 2015-2016: NES: Average cost of non-elective admission, short stay,	615.83
Face to Face attendance, Urology consultant	NHS Reference Costs 2015-2016: WF01A: National average unit cost of non-admitted face to face attendance, follow-up, Urology	100.00
General practitioner attendance	Unit Costs of Health and Social Care 2016	36.00
General practitioner telephone advice	Unit Costs of Health and Social Care 2016	14.60
Other health care advice	Unit Costs of Health and Social Care 2016	7.90

5.2.23 Within trial resource use costs

The specific costs considered in 5.2.22 were multiplied by use within the trial for the MRI ± targeted biopsy arm and the TRUS biopsy arm. The total cost in the MRI ± targeted biopsy arm was £161,682.50 and the total cost in the TRUS biopsy arm was £122,840.38. The resources that contributed the highest costs in the MRI ± targeted biopsy arm were the biopsy procedures, which cost £89,451.73 and the MRIs, which cost £50,430.00. In the TRUS biopsy arm, the resource that contributed the highest cost were the biopsy procedures which cost £96,767.08 (Table 5. 18).

5.2.24 Short-term cost-effectiveness outcomes from the PRECISION study

In the MRI ± targeted biopsy arm, the mean cost per patient at £642 [95% CI £597 to £686] was higher than the TRUS biopsy arm at £495 [95% CI £470 to £521], giving an incremental cost per patient in the MRI±TB arm of £147 [95% CI £95-£197]. The average cost per diagnosis of clinically significant cancer was lower in the MRI±TB arm at £1702 compared to £1919 in the TRUS biopsy arm. The incremental cost per additional case of clinically significant cancer diagnosed or clinically insignificant cancer avoided in the MRI±TB arm compared to the TRUS biopsy arm was £586 (Table 5. 19).

Table 5. 18: Within trial resource use and total costs

		MRI±TB arm		TRUS biopsy arm	
Resource	Unit Cost (£)	Number	Total Cost (£)	Number	Total Cost (£)
TRUS biopsy, outpatient	369.31	6	2215.86	197	72754.07
TRUS biopsy, day case	659.31	0	0.00	32	21097.92
Diagnostic multi-parametric MRI	205.00	246	50430.00	6	1230.00
MRI-TB, transrectal visually registered, outpatient	369.31	7	2585.17	0	0.00
MRI-TB, transperineal visually registered, outpatient	390.31	9	3512.79	0	0.00
MRI-TB, transrectal visually registered, day case	659.31	13	8571.03	0	0.00
MRI-TB, transperineal visually registered, day case	1158.31	8	9266.48	1	1158.31
MRI-TB, transrectal software-assisted, outpatient	396.78	96	38090.88	1	396.78
MRI-TB, transperineal software-assisted, outpatient	417.78	0	0.00	0	0.00
MRI-TB, transrectal software-assisted, day case	686.78	33	22663.74	0	0.00
MRI-TB, transperineal software-assisted, day case	1185.78	1	1185.78	0	0.00
Staging multi-parametric MRI scan, pelvis	205.00	0	0.00	39	7995.00
Transperineal template prostate biopsy, day case	1360.00	1	1360.00	1	1360.00
Staging CT scan, pelvis	119.00	33	3927.00	31	3689.00
Staging Bone scan	242.00	51	12342.00	37	8954.00
Staging PET-CT scan	436.00	0	0.00	1	436.00
Staging PET-MRI scan	484.00	0	0.00	1	484.00
A&E attendance	146.86	6	881.16	3	440.58
Hospital admission	615.83	7	4310.81	4	2463.32
Face to face attendance, Urology doctor	100.00	1	100.00	1	100.00
GP attendance	36.00	2	72.00	4	144.00
GP telephone advice	14.60	5	73.00	4	58.40
Other health care advice	7.90	12	94.80	10	79.00
Total Cost			**161682.50**		**122840.38**

Table 5. 19: Short-term cost-effectiveness outcomes from a UK health perspective

	MRI±TB arm	TRUS biopsy arm
Number of men (n)	252	248
Number of clinically significant cancers detected (n)	95	64
Number of clinically insignificant cancers detected (n)	23	55
Total cost, £	£161683	£122840
Mean cost per patient, £	£642 [95% CI 597-686]	£495 [95% CI 470-521]
Average cost per diagnosis of clinically significant cancer, £	£1702	£1919
Incremental cost per patient in MRI±TB arm compared to TRUS biopsy arm, £	£147 [95% CI 95-197]	
Additional numbers of clinically significant cancers diagnosed in the MRI±TB arm	31	
Additional number of significant cancers diagnosed in the MRI±TB arm on a per patient basis	0.12	
Additional numbers of clinically insignificant cancers avoided in the MRI±TB arm	32	
Additional numbers of clinically insignificant cancers avoided in the MRI±TB arm on a per patient basis	0.13	
Incremental cost per additional case of significant cancer diagnosed or insignificant cancer avoided, £	£586	

5.3 Discussion

5.3.1 Principle Findings

The PRECISION study demonstrated that in men with clinical suspicion of prostate cancer with raised PSA or abnormal digital rectal examination, MRI ± targeted biopsy was superior to TRUS biopsy in the detection of clinically significant cancer (12% higher detection rate) and superior in the avoidance of the detection of clinically insignificant cancer (13% lower detection rate). The MRI ± targeted biopsy pathway results in fewer men biopsied, fewer biopsy cores required and fewer side effects.

Clinicians appeared to value the certainty of the MRI ± targeted biopsy pathway more than the certainty of the TRUS biopsy pathway, as demonstrated by the lower proportion of men who had further diagnostic tests arranged after the result of the protocol diagnostic strategy.

Patients tended to prefer the MRI ± targeted biopsy pathway over the TRUS biopsy pathway as demonstrated by the fewer withdrawals in the MRI ± targeted biopsy arm after randomization. The good compliance to the trial protocol in the MRI arm demonstrated that clinicians and patients were comfortable in avoiding biopsy in the non-suspicious MRI and in avoiding the addition of systematic biopsy to targeted biopsy in men with suspicious MRIs.

Biopsy procedures in both arms were tolerated well, with immediate pain following the diagnostic tests and health-related quality of life at 30-days following the diagnostic test being similar in both arms. Serious adverse events were of low frequency in both arms.

The mean short-term cost per patient in the MRI arm was slightly higher than that of the TRUS biopsy arm, though due to costs saved from men avoiding biopsy altogether, costs were not significantly higher. In terms of cost-effectiveness, the average cost per diagnosis of significant cancer was slightly lower in the MRI arm due to its superior clinical performance. The incremental cost per diagnosis of an additional significant cancer or avoidance of the diagnosis of a clinically

insignificant cancer in the MRI arm was also relatively low at £586 per additional case.

5.3.2 Clinical implications and comparison to the literature

In men with clinical suspicion of prostate cancer who undergo multiparametric MRI of the prostate, just over a quarter had a non-suspicious MRI and were able to avoid a biopsy. Given that approximately one million men undergo biopsy in Europe and the USA every year, avoiding the use of an invasive test which carries discomfort and side effects is of great value [21]. In those with a suspicious MRI, there was most commonly only one suspicious lesion, leading to a biopsy procedure requiring fewer cores, that was less burdensome than seen in the TRUS biopsy arm. It has been demonstrated previously that MRI-targeted biopsy requires fewer cores [51] and as seen in the PRECISION study, this can contribute to fewer men experiencing side effects. This also has workforce capacity benefits as the pathologist has fewer specimens to analyse.

The MRI level of suspicion (PIRADSv2 score) showed a strong relationship to the likelihood of clinically significant cancer, with higher levels of suspicion leading to greater significant cancer detection. This has been demonstrated in previous studies which support the concept that the MRI level of suspicion is a strong predictor of the presence of clinically significant cancer [24].

Though the study was designed with a non-inferiority hypothesis, the MRI ± targeted biopsy arm had a detection rate for clinically significant cancer that was much higher than the TRUS biopsy arm and thus it was possible to demonstrate not only non-inferiority but also superiority of MRI ± targeted biopsy over TRUS biopsy. The superiority of MRI-targeted biopsy over TRUS biopsy in significant cancer detection has been demonstrated in previous meta-analysis [59] and single centre randomized trials [82], though conflicting results had been seen prior to this study. For instance, Baco *et al* and Tonttila *et al* had reported no difference in cancer detection between MRI-targeted biopsy and TRUS biopsy [83, 84]. Some of these previous trials were likely to be underpowered and there is risk of performance bias in studies which use a paired cohort design which can influence the observed results (Section 4.2.1).

PRECISION is the first adequately powered multi-centre randomized trial comparing the two modalities and the first study in which men with a suspicious MRI get a targeted biopsy only (without systematic biopsy) and men with a non-suspicious MRI get no biopsy at all. The randomized design allowed evaluation of the compliance to each of the diagnostic strategies and it is particularly important to note that patients and clinicians complied well with a pathway involving MRI risk stratification and MRI-targeted biopsy and following the protocol diagnostic test, not many patients underwent further diagnostic testing, which is in contrast to the TRUS biopsy arm.

As hypothesised, MRI ± targeted biopsy detected significantly fewer men with clinically insignificant cancer than systematic biopsy. This is consistent with the previous literature comparing MRI-targeted biopsy to systematic biopsy, for example in Haffner *et al* where 13% of insignificant cancer would have been avoided by an MRI-targeted biopsy strategy [52]. This reduction in insignificant cancer detection is due to fact that the MRI signal is highly associated with the presence of significant cancer. Thus, biopsies in the MRI arm are likely to be concentrated around areas more likely to harbour significant cancer whereas the biopsies in the TRUS biopsy arm are more likely to detect incidentally occurring insignificant cancer. Avoiding this insignificant cancer can be advantageous, as low-grade prostate cancer may not benefit from treatment, but inevitably some men do undergo treatment, which can result in harmful side effects [85, 86]. There is also the burden of worry to the patient and costs of ongoing follow up to health care services that a diagnosis of insignificant cancer causes [58, 87]. This comparison of clinically significant and clinically insignificant cancer detection rates highlights that MRI ± targeted biopsy could be a feasible alternative to TRUS biopsy as the standard of care in prostate cancer diagnosis as it may better identify patients who would benefit from treatment.

The short term absolute costs of the MRI ± targeted biopsy per patient are slightly higher than that of the TRUS biopsy pathway (£147 higher) and this relates to the additional cost of an MRI in all patients in the MRI arm and was also related to the fact that in this study a greater proportion of MRI-targeted biopsy procedures were done in a daycase theatre setting compared to TRUS biopsy, which was

primarily done in an outpatient clinic setting. The costs are particularly sensitive to the setting of the biopsy procedure, with daycase settings being more expensive due to the costs of theatre time and theatre staff. As clinicians gain more experience with the MRI-targeted biopsy technique, they may be able to adapt their practice to be primarily outpatient based, so this is a cost that could be reduced. Even for transperineal targeted biopsy, the use of local anaesthetic techniques [28] is becoming more common, so if an institution's preferred access route is transperineal, carrying out outpatient based procedures is feasible and could drive down the price of MRI ± targeted biopsy further. In the study, the additional costs of carrying out an MRI in each patient were offset partially by 28% of men avoiding biopsy and its costs altogether. Using MRI information to help identify a group of men who can avoid biopsy is likely to be critical in ensuring that the MRI-pathway is cost-effective.

Although absolute costs per patient were higher in the MRI ± targeted biopsy, MRI ± targeted biopsy was demonstrated to be cost-effective in this study, as the cost per diagnosis of significant cancer was slightly lower in the MRI ± targeted biopsy arm than the TRUS biopsy arm (£217 lower). When taking into account the additional clinically significant cancers identified and the additional clinically insignificant cancers avoided, the incremental cost of using MRI ± targeted biopsy was £586 per case of clinically significant cancer diagnosed or clinically insignificant cancer avoided. One way to put this incremental cost into perspective is to consider the example of the cost of managing a patient diagnosed with clinically insignificant cancer with active surveillance. In only the first year of surveillance the cost is £4412 (U.S. $ 6309) [58]. If the MRI ± targeted biopsy avoided the diagnosis of some truly clinically insignificant cancers, then it is clear that a £586 incremental cost is very low and use of the MRI ± targeted biopsy pathway is likely to be cost-effective.

Important points to consider are that the costs included in the analysis did not take into account further diagnostic tests arranged after the protocol test and we know that a reasonable proportion of men in the TRUS biopsy arm (15%) went on to have an additional MRI, whereas fewer men in the MRI arm (1%) went on to further testing. A further point is that the long-term cost-effectiveness is essential

to consider before making firm conclusions on the cost-effectiveness of the MRI ± targeted biopsy pathway from this trial. Though complex long-term health economic modelling was beyond the scope of this economic analysis, it is anticipated that through identifying more clinically significant cancer, less clinically insignificant cancer and fewer repeat biopsies, that MRI ± targeted biopsy should be cost-effective in the long term, as demonstrated by economic studies in the UK, Dutch, Canadian and US healthcare systems [88-91].

5.3.3 Strengths and limitations

PRECISION was a pragmatic multi-centre international randomized trial. The multi-centre nature of the study improves the generalisability of the findings and is one of the study's major strengths. A wide range of radiologists, urologists and pathologists took part in the study, a range of MRI protocols were permitted and a range of MRI-targeted biopsy techniques and access routes were allowed. The fact that the results were observed with this variation strengthens the findings of the study and allows the results to be more applicable to other institutions.

The performance bias seen with other studies adopting a paired cohort design is also mitigated by the randomized study design of PRECISION. This design meant that the accuracy of the MRI-targeted biopsy was not influenced by the performance of the TRUS biopsy or visa-versa. This design also allowed the feasibility of adopting the diagnostic pathway of MRI ± targeted biopsy as a replacement test to TRUS biopsy to be evaluated. For instance, when both MRI-targeted and TRUS biopsy are done in the same patients in a paired cohort study, it is difficult to evaluate acceptability, side effects and health economic outcomes of the MRI-targeted biopsy components of the test since every man gets both tests.

However, the study design does have some disadvantages. First, in prostate cancer in general and in both study arms, there is no ideal and easily applicable reference standard test for all men (see section 4.2). Thus, there is a reliance on the randomization process to lead to an equal number of men with significant cancer in each arm, with any differences in the number of cancers detected in each arm explained by the diagnostic test used. With a large sample size of 500

men and with there being no major differences in the baseline demographics between arms observed, it is likely that randomization was achieved satisfactorily and there is low risk of bias here, but nonetheless some risk is still present. This risk was mitigated by having a centrally administered randomization process by a recognised trials unit, thus ensuring appropriate sequence generation and strict allocation concealment.

Second, men with a non-suspicious MRI did not undergo biopsy and men with a suspicious MRI did not undergo systematic biopsy and could have had significant cancer missed. The men with non-suspicious MRIs have given consent for long term follow up in PRECISION, though emerging data from other studies provide us with reassurance in the meantime. Panebianco et al showed that the risk of detecting significant cancer in a cohort of 1255 patients with negative MRI followed up for 48 months was 4-5%, which is relatively low. In the PROMIS study the proportion of men who would have significant cancer missed by a negative MRI is higher, but none of these men had primary pattern Gleason 4 missed, which is reassuring.

With regards to the risk of missing clinically significant cancer in men with positive MRIs who do not undergo systematic biopsy in addition to targeted biopsy, other studies would suggest that the number of men missed is likely to be low, in the region of 0-10% [82, 92-94]. However even if some significant cancer was missed, the MRI ± targeted biopsy arm still detected more significant cancer than the TRUS biopsy arm and the purpose of the study was to evaluate the MRI ± targeted biopsy pathway as an alternative to TRUS biopsy. In that respect, the MRI ± targeted biopsy was superior.

Third relates to the quality control for the MRIs. This demonstrated that 78% of locally reported MRIs were concordant for biopsy decision with the central site quality control. This is lower than one might expect given the MRIs were reported with a validated scoring system such as PIRADSv2. This highlights a major challenge of the MRI pathway, which is better standardisation of the MRI reporting. However, the concordance seen is consistent with inter-reader agreement seen in previous multi-reader prostate MRI studies [95]. It is known

that MRI reporting is subject to a learning curve, which may have influenced this finding [96].

Fourth relates to the centres involved in the study. Although we deliberately allowed non-expert centres to take part in the study, approval for taking part in the study was given by the Chief Investigator based on sites providing us with audit data on their detection rates from biopsy. Approval was given if those detection rates were similar to the detection rates published in the literature from systematic reviews [59]. If detection rates were lower than expected then the site's MRIs were reviewed and an in-person site visit could take place to assess local performance quality. This means that on average the centres taking part in the study were likely to have at least reasonable experience in prostate MRI, thus other centres should be encouraged to evaluate their own performance data to see if it is comparable to the published literature before changing their diagnostic approach. That being said, it is clear from the clinician experience in the study that the MRI-targeted biopsy operators had relatively modest experience (median of 100 procedures previously performed) to the TRUS biopsy operators (median of 750 procedures performed) and the superior cancer detection rates were achieved despite this.

Fifth relates to lack of blinding of investigators and participants in the study. Though the primary outcome of significant cancer detection is likely to be at low risk of bias, there is the potential that the pathologist would know which arm the patient was in and thus may be consciously or subconsciously influenced in their reporting of the outcome. Of note, none of the pathologists were the principle investigators of their site, were not involved in decisions for the site to take part in the study and are unlikely to have any conscious bias in favour of one technique or the other. Practically it would be very challenging to blind the pathologists from knowing which arm a patient has been allocated to. This is because for clinical reasons, the pathologist needs to know the location of the cores so that they can include this in their report. This localisation information is needed in the pathology report by the treating urologist to make appropriate treatment decisions. If the cores are not from the typical TRUS biopsy locations, the pathologist will know that the biopsy is an MRI-targeted biopsy. In addition, they will expect a typical

number of cores from the TRUS biopsy (10-12) and given the majority of men in the MRI arm had 1 or 2 suspicious lesions, they would be able to tell which were from MRI-targeted biopsy as there would be 8 or fewer cores typically. Quality control of pathology reporting showed that the central pathologist agreed with the local site pathologist 88% of the time, which is consistent with the expected concordance in the published literature [97]. A small proportion of specimens were upgraded or downgraded, though this was non-differential between arms. Of note, the statistician who analysed the data was from an independent group and derived the statistical analysis plan before having access to the data. The analysis was also checked independently by a second statistician from the independent group, thus statistical analysis was at low risk of bias.

5.3.4 Research implications

These results highlight several areas for future research. The first would be improving the standardisation of MRI reporting. There are limitations in inter-reader reproducibility with the PIRADSv2 scoring system which have been highlighted by the quality control in PRECISION. When looking at the PROMIS study which used the 1-5 Likert scale of suspicion without using the rigid PIRADSv2 criteria (section 1.10), the inter-reader reproducibility was similar to that seen here. The Likert scale used in PROMIS was based on subjective decision making by the radiologist and was more flexible in allowing scores of suspicion the be derived. This allows radiologists to take into account scenarios that the PIRADSv2 scoring system does not account for. An example would be a peripheral zone lesion that is only contrast enhancing and does not show up on the T2-weighted or diffusion weighted sequences. On PIRADSv2 this could only be scored a 1 or 2 and thus would not undergo biopsy but on the Likert scale this could be scored a 3 or higher on the 1-5 scale and could be recommended to undergo biopsy. It is clear that further research into standardising the MRI reporting system so that scenarios like this are taken into account for would help improve the reliability of the MRI reporting and the detection of significant cancer.

A second area for future research would be focussing on the training of urologists and radiologists to use and interpret MRI information. Often the urologist uses

MRI information to perform a targeted biopsy or targeted treatment without actually being able to understand the MRI images for themselves. Given the small size of the lesions demonstrated in this study and the small margin of error, to be able to accurately target biopsies, an understanding of the lesion location on the MRI images is important. It is currently not known whether urologists would be able to adapt and learn this new skill well or not. For radiologists, it is known that a learning curve in MRI interpretation exists and standardised and validated teaching programs should be developed to disseminate knowledge to ensure high quality MRI reporting.

A third area for research would be to evaluate the capacity of health services to deliver an MRI-based diagnostic pathway and changes that may need to be made to accommodate such a change. With the adoption of such a pathway, the number of men undergoing prostate MRI scans will increase significantly which poses questions on the capacity of existing infrastructure to cope with such changes. It may be the case that dedicated MRI scanners for prostate scanning are required at busy centres to cope with the demand required, as is the currently the situation at some academic centres. In addition, potential changes in the MRI protocols may be required to optimise the efficiency of the scan without compromising the quality of the imaging.

5.3.5 Conclusions

The PRECISION study has shown that MRI ± targeted biopsy detects more clinically significant cancer and less clinically insignificant cancer than TRUS biopsy, leads to fewer men being biopsied and requires fewer cores. It achieves these goals whilst remaining cost-effective in the short term. These findings would support the adoption of MRI ± targeted biopsy instead of TRUS biopsy as the standard of care for prostate cancer diagnosis.

5.4 Statement of Contribution

A detailed statement of contribution has been specified in section 4.28.

5.5 Related Publication

Kasivisvanathan V, Rannikko AS, Borghi M, Panebianco V, Mynderse LA, Vaarala MH, Briganti A, Budaus L, Hellawell G, Hindley RG, Roobol MJ, Eggener S, Ghei M, Villers A, Bladou F, Villeirs GM, Virdi J, Boxler S, Robert G, Singh PB, Venderink W, Hadaschik BA, Ruffion A, Hu JC, Margolis D, Crouzet S, Klotz L, Taneja SS, Pinto P, Gill I, Allen C, Giganti F, Freeman A, Morris S, Punwani S, Williams NR, Brew-Graves C, Deeks J, Takwoingi Y, Emberton M, Moore CM, Collaborators PSG.

MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis.

N Engl J Med. 2018 May 10;378(19):1767-1777.

Chapter 6 Assessing the ability of Urologists to learn how to interpret Prostate MRI information

The findings from the work in this chapter have been published in *European Urology* [98].

6.1 Introduction

We have learnt that multi-parametric MRI has a key role in the diagnosis and management of prostate cancer. Level 1 evidence from the PRECISION trial, PROMIS trial and others demonstrate the benefit of a diagnostic pathway involving MRI [24, 74, 82, 92, 99, 100]. When a novel technology becomes increasingly integrated into the care pathway it is both important and desirable that the workforce be equipped to maximise the value of that technology for their patients.

One of the limitations highlighted from the PRECISION trial was that clinicians would need to be trained to use prostate MRI, not only to inform the decision for and conduct of MRI-targeted procedures, but to inform patient discussions in clinic. We know that prostate MRI can play an important role in determining which men need a biopsy [24] and in informing the conduct of an MRI-targeted biopsy [63, 101]. In the majority of settings, it is the Urologist who performs the biopsy. To perform an accurate MRI-targeted biopsy, a Urologist must have knowledge of anatomy of the prostate on MRI, ability to localise lesions in relation to anatomical landmarks such as the prostatic urethra, base, apex and seminal vesicles, ability to spatially relate that information to the real-time imaging being used (for example, real-time transrectal ultrasound imaging) and to be able to direct their biopsy needle accurately into areas of suspicion.

Despite this fundamental need to be able to interpret the MRI information, Urologists do not get formal training in prostate MRI interpretation. The radiologist who reports the prostate MRI is not typically with the Urologist when they perform the MRI-targeted biopsies and whilst they can communicate this MRI information to the Urologist with diagrams, prose reports or marking lesions on imaging, it is

the biopsy operator who ultimately makes the decision on where to place the biopsy cores. Even if image fusion software is used, it is still necessary for operators to be able to contour the prostate and lesion on the ultrasound and the MRI, which determines the location that the lesion will appear in on the ultrasound during the biopsy procedure. During an image-fusion biopsy, the judgement of the Urologist, as used during a visual registration technique, is still important. As the shape and position of the prostate in the pelvis during the MRI scan when the patient is lying flat is different to that seen during the real-time ultrasound guided procedure when the patient's hips are usually flexed, the image-fusion software can give registration errors [102]. These errors, if not adjusted for by the operator's judgement, can lead to biopsy cores taken several millimetres away from the actual prostate cancer lesion.

Beyond MRI-targeted biopsy, MRI information can also play a key role for Urologists in treatment planning for men diagnosed with prostate cancer. Improvement in the precision of diagnosis of a disease can often lead to an improvement in the precision and range of treatments offered to patients. Men on active surveillance can undergo interval MRI scans [103] where MRI lesions are monitored over time and if progressing can undergo repeat biopsy and treatment. An appreciation of how the MRI signal can change over time and the implications that this has for treating patients would be an important skill to have for Urologists.

During radical prostatectomy, use of MRI can help plan a nerve-sparing approach [104-106]. Where disease is close to the capsule on one particular side of the prostate, clinicians may wish to concentrate on oncological cure and take wide margins rather than nerve sparing on that side. If a particular side of the prostate is free of disease, this may encourage clinicians to adopt a nerve sparing approach on that side. This approach may help in optimising functional outcomes such as erectile function following radical treatment. Focal therapy, a more recently introduced treatment option, can also be used to treat prostate cancer lesions using an appropriate energy source and has shown to offer good functional outcomes and reasonable short to mid-term outcomes [107, 108]. A

key principle in focal therapy is being able to locate the MRI lesion and being able to leave appropriate margins during treatment.

Thus, it is important for urologists managing patients with prostate cancer, particularly those performing prostate biopsy and prostate interventions, to be able to understand and use MRI information to a high standard. It is not known however, whether prostate MRI interpretation is a skill that can be gained by urologists as this skill is not typically part of their teaching curriculum. Thus, I devised a standardised MRI learning module for urologists that incorporated an assessment component. I aimed to assess the ability of urologists to interpret prostate MRI to detect clinically significant prostate cancer and assess whether a training course in prostate MRI could improve this. If significant improvement were to be observed, it would support the incorporation of prostate MRI teaching into the urologists' routine training. I hypothesised that a short training course would be able to improve the Urologist's ability to interpret clinically significant cancer on prostate MRI.

6.2 Methods

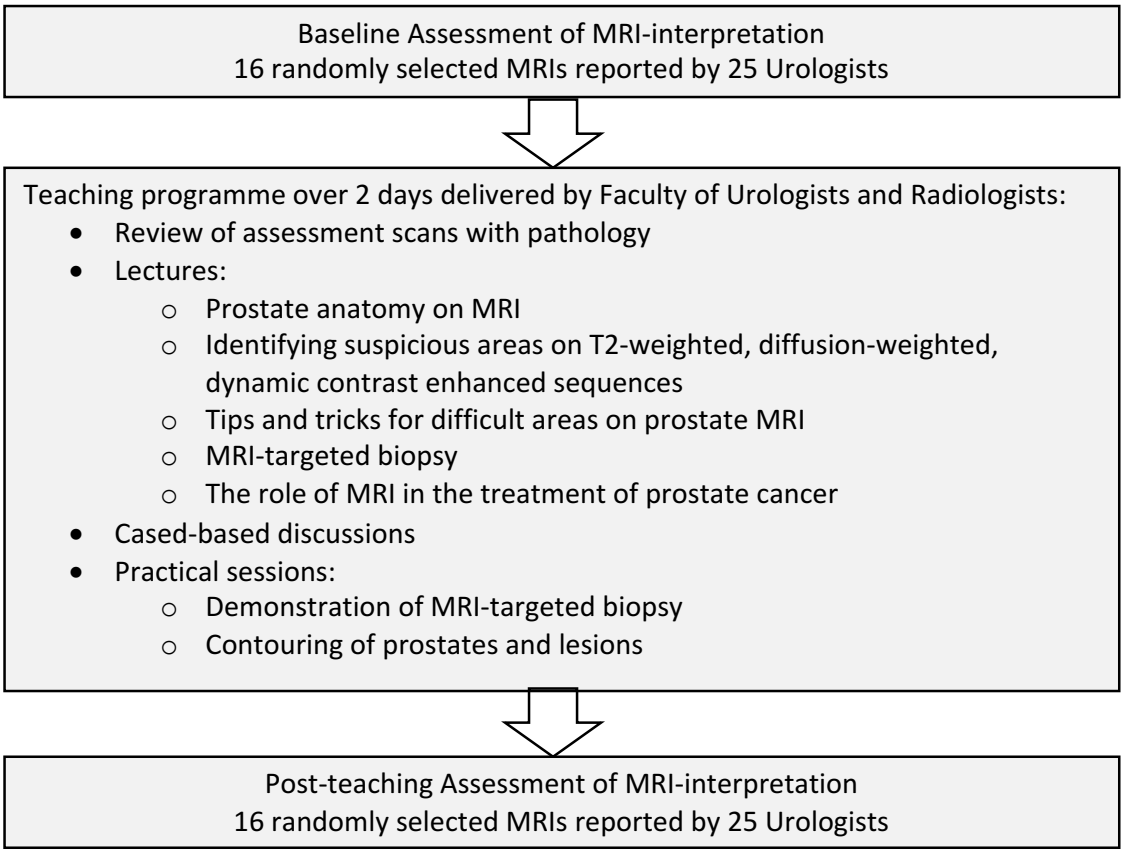
6.2.1 Participants

A Prostate MRI Course was advertised nationally to urologists and urological trainees working in the UK. No prior experience of Prostate MRI was necessitated, though baseline experience level was ascertained at the start of the course.

6.2.2 Training course

Using the experience gained by our team from annual prostate MRI courses delivered by radiologists for radiologists over the previous 5 years, a novel Prostate MRI course for Urologists was delivered at our institution to participants over 2 days in September 2016 (Figure 6. 1).

Figure 6. 1: The structure of the 2-day training course.



Teaching was given in didactic lectures, case based presentations, practical reporting sessions, test sessions with individual feedback and review of test cases. Prior to the course, participants were sent background reading on the conduct and reporting of Prostate MRI [46, 48]. Computers were provided for each participant, with prostate MRI scans pre-loaded and displayed using an open source viewing platform (OsiriX Lite, version 7.5.1, OsiriX Imaging Software, Geneva, Switzerland).

Participants took part in a 2-hour baseline test session at the start of the course. They independently reviewed 16 prostate MRI scans, recording the likelihood of suspicion of clinically significant cancer on a pre-prepared scoring proforma. Participants were blinded to the radiology and pathology reports for that patient. Anonymised clinical details including age, PSA, digital rectal examination result and previous biopsy details were provided. Participants gave each prostate an overall score of suspicion on the 1-5 Likert scale [24, 46] for the likelihood of harbouring clinically significant cancer as highly unlikely (1), unlikely (2), equivocal (3), likely (4), highly likely (5). Prostates were also scored by quadrant, the likelihood of extracapsular extension and urethral sphincter involvement on a 1-5 Likert scale. Participants indicated their overall confidence in scoring each case on a 1-5 Likert scale.

After the test, cases were reviewed with the participants by an expert radiologist, individual feedback was given to participants and the pathology results were revealed. Further teaching content for the course was then delivered over the next 2 days including lectures on prostate anatomy, identifying suspicious areas on prostate MRI, understanding the different sequences on MRI, scoring systems for prostate MRI reporting, MRI-targeted biopsy of the prostate, contouring the prostate and suspicious lesions, using MRI information in real cases to influence patient management and minimum standards for carrying out prostate MRI. At the end of the second day, a second different set of 16 scans were independently reviewed and scored by the participants under the same test conditions over 2 hours, under test conditions.

6.2.3 Faculty members

Faculty members were radiologists and urologists who were part of our institution, an academic centre experienced in prostate MRI. Faculty members had taken part in dedicated weekly prostate MRI multi-disciplinary team meetings where radiology and pathology information is used to make patient treatment management decisions. They were part of a team experienced in MRI-targeted biopsy, focal therapy and radical prostatectomy with published outcomes [24, 53].

6.2.4 Prostate MRI scans

Anonymised pre-biopsy multi-parametric MRIs were chosen from an institutional database of men undergoing pre-biopsy MRI followed by transperineal template prostate biopsy. Men had been originally referred with clinical suspicion of prostate cancer based on raised PSA and/or abnormal digital rectal exam and had either had no prior biopsy or prior negative TRUS biopsy. In those with prior negative TRUS biopsies, MRI was carried out at least 3 months following previous biopsy to minimise post-haemorrhagic artefact. MRI scans had been carried out on a 1.5T or 3T machine with pelvic phased array coil, including T2-weighted, diffusion-weighted and dynamic contrast enhanced sequences (Table 6. 1). 32 scans with full MRI sequences were chosen by random selection, without replacement, from the database, so that the 16 scans for the baseline and end of course test were likely to be of a similar level of difficulty. Prostate MRIs were also scored by one of two radiologists, with 9 and 10 years of experience in Prostate MRI, who were typically reporting more than 1000 scans per year.

Table 6. 1: MRI protocols for the scanners used in the study

MRI manufacturer	Siemens	Philips
Model	Avanto	Achieva
Filed Strength	1.5T	3T
Coils	Pelvic phased array	Pelvic phased array
Sequences	T2-weighted Dynamic contrast enhanced Diffusion weighted	T2-weighted Dynamic contrast enhanced Diffusion weighted
T2-weighted sequences Planes acquired Slice Thickness (axial) Voxel size (axial)	 Axial, coronal 3mm 0.391 x 0.391 x 3.45 mm	 Axial, coronal 3mm 0.375 x 0.375 x 3.3mm
Dynamic Contrast enhanced Sequences Temporal resolution Slice Thickness Voxel size Fat saturation (FS)/subtraction(SUB) Power injector Injection rate	 11 s 3mm 0.677 x 0.677 x 3mm Yes (FS) Yes 3mls/s	 11 s 3mm 0.938 x 0.938 x 3mm Yes (FS) Yes 3mls/s
Diffusion weighted imaging sequences B-values used ADC threshold applied? DWI combinations Slice Thickness Voxel size	 0,150,500, 1000,1400 Yes Multi-b value, ADC & high b 5mm 1.51 x 1.51 x 5 mm	 0,150,500, 1000,2000 Yes Multi-b value, ADC & high b 5mm 0.98 x 0.982 x 5 mm
Bowel relaxant used	Yes	Yes

6.2.5 Reference standards

All men had undergone 5mm transperineal template mapping prostate biopsy plus or minus MRI-targeted biopsy as described in Chapter 2 and previously [23, 53]. The presence of a single core containing prostate cancer with Gleason grade 3+4 or greater and/or a maximum cancer core length of 4mm or greater was the

a priori chosen definition of clinically significant cancer [54]. The pathology was originally reported by one of two pathologists, with 11 and 20 years of experience in reporting prostate specimens, each reporting approximately 100 prostate specimens per year.

6.2.6 Primary outcome

The primary outcome was the cohort's change in average area under the curve (AUC) for detection of clinically significant cancer, at the whole gland level, before and after teaching [98].

6.2.7 Secondary outcomes

Secondary outcomes included the change in average AUC for detection of clinically significant cancer at the quadrant level, the proportion agreement beyond chance for extracapsular extension (ECE) of prostate cancer, the proportion agreement beyond chance for urethral sphincter involvement compared to the expert radiologist and the confidence of the participant in scoring the prostate MRI. Subgroup analyses were carried out to ascertain the change in average AUC for participants categorised by their relative prior experience in prostate MRI within the group and by anatomical division of the prostate into peripheral zone and transition zone.

6.2.8 Statistical methods

Continuous variables are presented as median and interquartile ranges (IQR) defined as [1st quartile, 3rd quartile]; categorical data are presented as frequencies and percentages. Differences between groups in continuous variables were assessed by Wilcoxon statistic. The overall performance in identifying clinically significant cancers was evaluated by the Receiver Operator Characteristic (ROC) and the associated AUC. The urologist's score of suspicion was compared to the histopathological reference standard of transperineal template biopsy and MRI-targeted biopsy for that prostate or part of the prostate.

To take into account of possibly dependencies among measurements coming from the same reader, cases and/or quadrants, ROC curves were based on Generalized Linear Mixed Models (GLMM) with random effects on readers, cases and/or quadrants; this approach generalizes the Obuchowski–Rockette method [109] and is also described by Liu et al. [110] [98]. For each ROC curve and AUC value, 95% confidence band was computed by stratified Bootstrap (B=50,000 samples) and adjusted percentile [98, 111].

To put AUCs into context, an AUC of 0.5 would mean that the chances of correctly identifying significant cancer were similar to the chances of correctly guessing which side a flipped coin would land on. An AUC > 0.5 would suggest that the urologist was better than chance at identifying significant cancer and an AUC < 0.5 would suggest that the urologist was worse than chance at identifying significant cancer.

Agreement between measurements by the expert radiologist and urologist for sphincter involvement and extracapsular extension was evaluated by means of weighted Kappa statistics in which disagreements are weighted according to their squared distance from perfect agreement [112].

Exact p-values were assessed by means of conditional permutation procedure to avoid any distributional assumption or asymptotic approximation [113].

The analyses were performed in R environment (www.R-project.org, ver 3.4.1) and OR-DBM MRMC software (Medical Image Perception Laboratory, http://perception.radiology.uiowa.edu, ver 2.5).

6.2.9 Ethics

Ethical exemption applied for this study as per UK NHS Health Research Authority and National Research Ethics Service guidance.

6.3 Results

6.3.1 Participant characteristics

Seventeen out of the 25 (68%) participants were urologists at consultant level with the remaining 8 being trainees. The median number of prostate MRIs looked at by participants in the previous 3 years was 100-199, the median number of MRI-targeted prostate biopsies performed in the previous 3 years by the participants was 1-24 and 18/25 (72%) regularly attended a multi-disciplinary team meeting where prostate MRI imaging was discussed with a radiologist (Table 6. 2).

6.3.2 Patient characteristics

All of the MRIs were carried out in either biopsy naïve (14/32, 44%) men or those with prior negative TRUS biopsies (18/32, 56%). Age, PSA, number of men with abnormal digital rectal examination, prostate volume and radiologist Likert score distribution was similar in both Test 1 and Test 2 (Table 6. 3). Clinically significant cancer was detected in 18/32 (56%) of men overall.

6.3.3 Average area under the curve for detection of clinically significant cancer on a whole gland level

Individual participant's AUCs for detection of clinically significant cancer improved for every participant after teaching (Table 6. 2). There was a significant improvement in average AUC from baseline (0.60 [95% CI 0.55-0.65]) to post-teaching (0.77 [95% CI 0.72-0.82], difference 0.17, [95% CI 0.10-0.24]), $p < 0.0001$ (Figure 6. 2).

6.3.4 Agreement with radiologist on extra-capsular extension and urethral sphincter involvement

There was poor agreement beyond chance with the expert radiologist for likelihood of extra-capsular extension of disease at baseline (weighted kappa 0.104, $p = 0.0002$), though this improved after teaching to fair to moderate

agreement beyond chance (weighted kappa 0.443, p <0.0001), with improvement in agreement between the two tests being statistically significant (difference 0.339, p <0.0001). For urethral sphincter involvement, each case in the baseline test was scored by the radiologist as being extremely unlikely to involve the urethral sphincter so it was not possible to determine a weighted kappa. In test 2, the agreement beyond chance for urethral sphincter involvement was fair to moderate (weighted kappa 0.330, p < 0.0001).

6.3.5 Participant's confidence in scoring the MRI scans

The participants mean confidence in scoring the scans improved from baseline at test 1 (3.19, SD±1.05) to post-teaching (3.53, SD±0.86), p < 0.0001.

Table 6. 2: Participant experience and individual area under the curves for detection of significant cancer for Test 1 and Test 2

MRI-TB = MRI-targeted biopsy; MDT = multi-disciplinary team meeting; AUC = area under the curve for detection of clinically significant prostate cancer at whole gland level

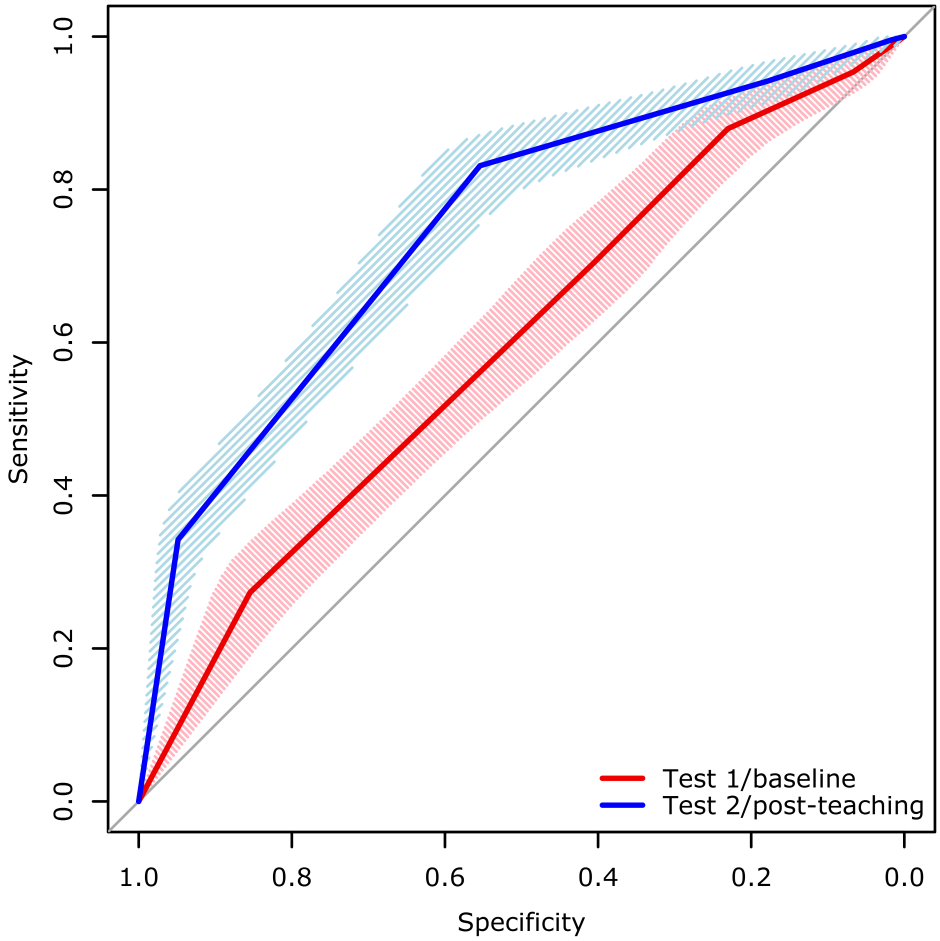
Participant Number	Level	Number of MRIs looked at in previous 3 years	Number of MRI-TB performed in previous 3 years	Regularly attending MDT in past 3 years	AUC test 1 (baseline)	AUC Test 2 (after teaching)
1	Trainee	25-99	1-24	No	0.50	0.81
2	Trainee	25-99	1-24	No	0.53	0.81
3	Consultant	25-99	25-99	Yes	0.52	0.73
4	Trainee	1-24	0	No	0.54	0.78
5	Trainee	25-99	1-24	No	0.52	0.78
6	Consultant	100-199	25-99	Yes	0.54	0.70
7	Consultant	1-24	0	Yes	0.55	0.57
8	Trainee	25-99	1-24	Yes	0.52	0.82
9	Consultant	100-199	0	Yes	0.53	0.77
10	Consultant	100-199	25-99	Yes	0.65	0.68
11	Consultant	100-199	1-24	No	0.54	0.70
12	Consultant	100-199	100-199	Yes	0.63	0.65
13	Consultant	500-999	0	Yes	0.52	0.74
14	Trainee	1-24	1-24	No	0.54	0.57
15	Trainee	200-499	25-99	Yes	0.66	0.83
16	Trainee	100-199	25-99	Yes	0.53	0.74
17	Consultant	25-99	1-24	Yes	0.51	0.58
18	Consultant	100-199	1-24	Yes	0.54	0.80
19	Consultant	500-999	25-99	Yes	0.60	0.77
20	Consultant	1-24	1-24	No	0.52	0.77
21	Consultant	25-99	25-99	Yes	0.56	0.65
22	Consultant	100-199	1-24	Yes	0.65	0.82
23	Consultant	25-99	1-24	Yes	0.53	0.76
24	Consultant	100-199	0	Yes	0.51	0.77
25	Consultant	500-999	500-999	Yes	0.51	0.66
Average area under the curve for cohort [95% CI]:					0.60, [95% CI 0.55-0.65]	0.77, 95% CI [0.72-0.82]

Table 6. 3: Summary characteristics of the patients used in the test cases

Characteristic	Test 1	Test 2
Age, years (mean±SD)	63.4±4.9	62.6±6.9
PSA, ng/ml (median, IQR)	7.0 (3.5-9.9)	7.0 (5.9-12.6)
Number with abnormal digital rectal exam (n, %)	3 (19%)	3 (19%)
Number of biopsy naïve men (n, %)	6 (38%)	8 (50%)
Number of men with prior negative TRUS biopsy (n, %)	10 (63%)	8 (50%)
Expert Uro-radiologist assessment		
Number of MRI lesions (n)	14	13
MRI lesion volume, median (mls)	0.6 (0.17-0.80)	0.7 (0.15-1.6)
Prostate volume (median, IQR)	34.5 (27.5-59.9)	36.5 (28.2-51.5)
Number of men with Likert score 1	0	0
Number of men with Likert score 2	3	3
Number of men with Likert score 3	4	4
Number of men with Likert score 4	4	4
Number of men with Likert score 5	5	5
Number of men with clinically significant cancer (Gleason 3+4 or greater and/or maximum cancer core length 4mm or greater) (n,%)	9 (56%)	9 (56%)

Figure 6. 2: Average area under the curve for detection of clinically significant cancer at baseline (test 1) and post-teaching (test 2) at the whole gland level

Reproduced, with permission, from [98]. The red line represents the area under the curve for detection of clinically significant cancer from test 1 at baseline (0.60 [95% CI 0.55-0.65]). The blue line represents the area under the curve for detection of clinically significant cancer from test 2, post teaching (0.77 [95% CI 0.72-0.82]), $p < 0.001$. The shaded areas represent the 95% confidence intervals for the area under the curve.

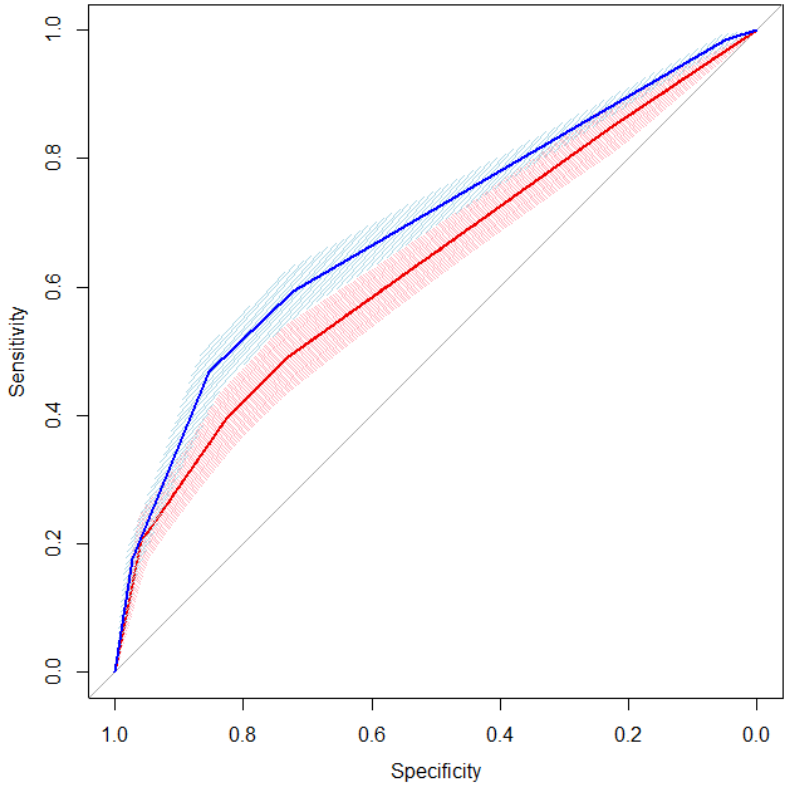


6.3.6 Average area under the curve for detection of clinically significant cancer on a quadrant level

When looking at the ability of Urologists to localise disease on a quadrant level, the improvement in average AUC for detection of significant cancer before (baseline AUC 0.63 [95% CI 0.60-0.63]) and after teaching (post-teaching AUC 0.69 [95% CI 0.67-0.69]) also improved (difference 0.06, [95% CI 0.04-0.08], p =0.007), Figure 6. 3.

Figure 6. 3: Average area under the curve for detection of clinically significant cancer at baseline (test 1) and post-teaching (test 2) at quadrant level

The red line represents the area under the curve for detection of clinically significant cancer from test 1 at baseline (0.63 [95% CI 0.60-0.63]). The blue line represents the area under the curve for detection of clinically significant cancer from test 2, post teaching (0.691 [95% CI 0.67-0.69]), p = 0.007. The shaded areas represent the 95% confidence intervals for the area under the curve.



6.3.7 Subgroup analysis: cancer detection by anatomical location of prostate and by prior experience level of participants

When looking at the subgroups, in the peripheral zone, the average AUC for detection of clinically significant cancer improved from baseline (AUC 0.59 [95% CI 0.54-0.64]) to post-teaching (AUC 0.73 [95% CI 0.68-0.78], p=0.0003). In the transition zone, the average AUC for detection of clinically significant cancer improved from baseline (AUC 0.60 [95% CI 0.53-0.67]) to post-teaching (AUC 0.68 [95% CI 0.61-0.74]), though this difference was not statistically significant (p = 0.13) (Table 6. 4).

Table 6. 4: Average area under the curve for detection of clinically significant cancer in sub-groups at baseline (test 1) and post-teaching (test 2)

AUC = average area under the curve for the detection of clinically significant prostate cancer

*Low prior experience = Looked at fewer than 100 MRIs and performed fewer than 25 MRI-targeted prostate biopsies in the previous 3 years

†Moderate prior experience = Looked at between 100-200 MRIs and performed 25-100 MRI-targeted prostate biopsies in the previous 3 years

§High prior experience = Looked at 200 or more MRIs and performed more than 100 MRI-targeted prostate biopsies in the previous 3 years

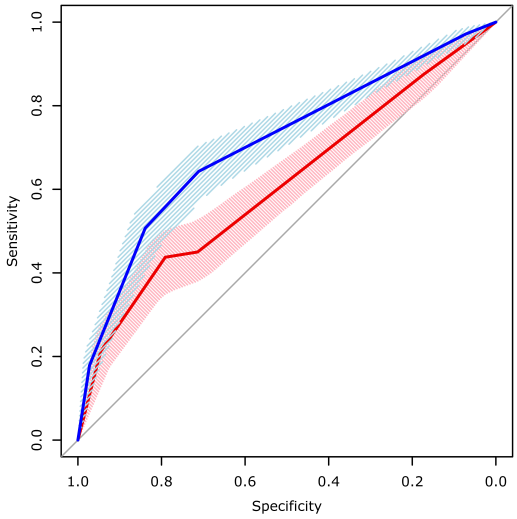
Sub-group	Test 1 AUC	Test 2 AUC	p-value for difference in AUC (Test 2-Test 1)
Transition zone	0.60 [95% CI 0.53-0.67]	0.68 [95% CI 0.61-0.74]	p = 0.14
Peripheral zone	0.59 [95% CI 0.54-0.65]	0.73 [95% CI 0.68-0.78]	p = 0.0003
Low prior experience*	0.62 [95% CI 0.53-0.71]	0.75 [95% CI 0.68-0.82]	p = 0.023
Moderate prior experience†	0.64 [95% CI 0.56-0.72]	0.73 [95% CI 0.65-0.81]	p = 0.13
High prior experience§	0.64 [95% CI 0.51-0.75]	0.83 [95% CI 0.74-0.91]	p = 0.009

The average AUC for detection of significant cancer by the subgroup of prior MRI experience level is depicted in Figure 6. 4.

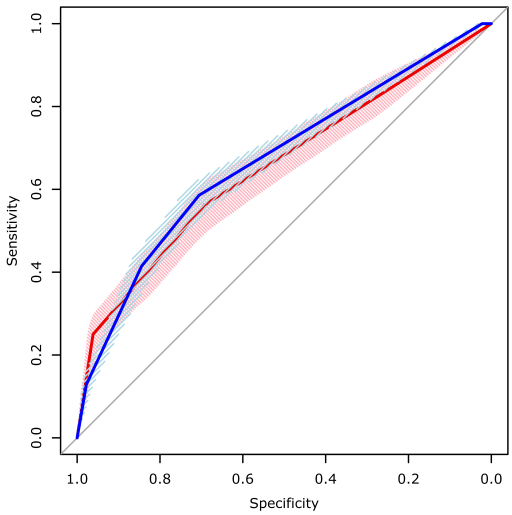
Figure 6. 4: Average area under the curve (AUC) for detection of clinically significant cancer at baseline (test 1) and post-teaching (test 2) for participants of different experience level of prostate MRI prior to the course.

The red lines represent the area under the curve for detection of clinically significant cancer from test 1 at baseline. The blue lines represent the area under the curve for detection of clinically significant cancer from test 2, post teaching. The shaded areas represent the 95% confidence intervals for the area under the curve.

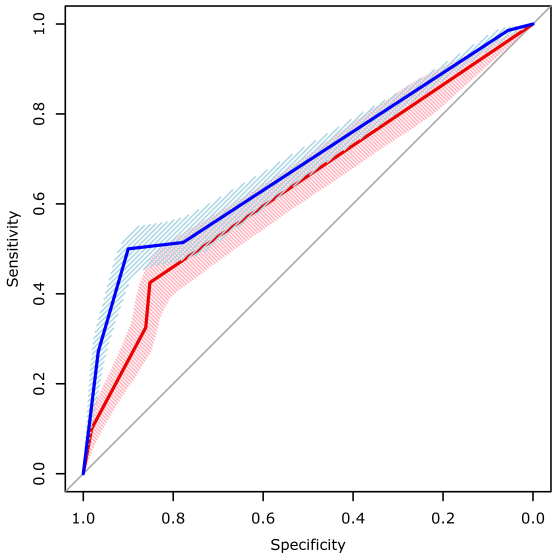
(a) Least prior experience



(b) Moderate prior experience



(c) Most prior experience



(a) Least prior experience of prostate MRI (Looked at fewer than 100 MRIs and performed fewer than 25 MRI-targeted prostate biopsies in the previous 3 years). Baseline area under the curve was 0.62 [95% CI 0.53-0.71] and post-teaching area under the curve was 0.75 [95% CI 0.68-0.82], p = 0.023.

(b) Moderate prior experience of prostate MRI (Looked at between 100-200 MRIs and performed 25-100 MRI-targeted prostate biopsies in the previous 3 years). Baseline area under the curve was 0.64 [95% CI 0.56-0.72] and post-teaching area under the curve was 0.75 [95% CI 0.68-0.82], p = 0.13

(c) Most prior experience of prostate MRI (Looked at 200 or more MRIs and performed more than 100 MRI-targeted prostate biopsies in the previous 3 years). Baseline area under the curve was 0.64 [95% CI 0.51-0.75] and post-teaching area under the curve was 0.83 [95% CI 0.74-0.91], p = 0.009.

In summary, there was a statistically significant improvement in average AUCs for those with the least (looked at fewer than 100 prostate MRIs and performed fewer than 25 MRI-targeted biopsies in the previous 3 years) and the most (looked at 200 or more MRIs and performed more than 100 MRI-targeted prostate biopsies in the previous 3 years) prior experience and though there was an improvement for those with moderate experience, this was not statistically significant (p=0.13).

6.3.8 Expert radiologist's area under the curve

The AUC for the detection of clinically significant cancer of the expert radiologist for the baseline test was 0.87 [95% CI 0.77-0.98] and for the post-teaching test was 0.88 [95% CI 0.77-0.98].

6.4 Discussion

The main findings of this study are that urologists can improve their ability to correctly identify and localise clinically significant cancer on multiparametric MRI after a short teaching course. Their agreement with expert radiologists in determining extra-capsular extension and confidence in assessing MRI also improves with training. This is the first time that this has been assessed in a group of urologists.

A previous cohort of fellowship-trained radiologists in a study in the USA also demonstrated improvement in AUC after teaching, with average AUC for detection of significant prostate cancer at baseline of 0.52 and after didactic lectures of 0.66 [114]. Whilst both cohorts showed a consistent improvement in AUC, the current cohort appeared to perform better. Unlike the previous cohort which used only T2-weighted imaging, this study used multi-parametric MRI, with T2-weighted, diffusion-weighted and dynamic contrast enhanced imaging, which has shown to improve cancer detection [45]. In addition, in the previous cohort, it was not apparent that the post-teaching MRIs were selected at random, whereas in this cohort both baseline and post-teaching MRIs were randomly selected to ensure difficulty between both tests was similar. The improvement in performance seen after only a small number of MRI scans was consistent with other studies, where 35-40 scans were shown to improve the sensitivity for detection of cancer [115, 116] and in another where the diagnostic performance for detection of ECE improved after 40 scans [117]. This highlights that performance can be improved with even quite short training exposure.

In the current study, the ability to detect cancer by the urologists was not as good as the expert radiologists, which would be expected given the learning curve required for prostate MRI interpretation and the experience of the radiologists involved in this study [116]. However, it is not expected or intended that Urologists report prostate MRI instead of radiologists. Given the advances in standards of conduct of multiparametric MRI and increasing importance that MRI plays in the management of patients with prostate cancer, it is essential for urologists to embrace this development and learn to use MRI information.

Though we require expert radiologists to report prostate MRI, better understanding of the information gained from multiparametric MRI will equip urologists to perform accurate targeted biopsy and targeted treatments and allow them to actively engage in the delivery of multi-disciplinary care that can benefit their patients.

Parallels can be drawn to other disease areas, for example renal colic and renal cancer. In renal colic, a surgeon would not likely take a patient to theatre to perform an operative procedure without having seen the imaging and reviewed the position of the stone themselves. In renal cancer, a decision for nephrectomy and decisions between partial or radical nephrectomy and between open or minimally invasive surgery would not be made without the surgeon reviewing the imaging themselves. Likewise, in prostate cancer, I would suggest that a surgeon should not make a decision for biopsy, perform a biopsy or perform a targeted treatment without having reviewed the imaging themselves. These results would support efforts to integrate Prostate MRI teaching courses into the training of urologists managing patients with prostate cancer.

The sub-group analyses should be interpreted with caution due to the small numbers involved. However, improvements in AUC for detecting significant cancer were more pronounced in the peripheral zone, which is consistent with known challenges for detection of cancer in the transition zone [118]. Radical prostatectomy series show us that the majority of prostate cancer is located in the peripheral zone [119], consistent with the area that participants showed the greatest improvement. Expert groups are attempting to optimise methods of assessment in the transition zone [120] and it is recognised that this is a challenging area for reporting. Though participants showed an improvement in assessing this specific area, this improvement did not reach statistical significance, though overall on a whole gland level, when taking into account both the transition and peripheral zone, participants did improve statistically.

The participant's baseline experience level of prostate MRI prior to the course varied. It is important to relate their performance to their baseline level of experience, particularly because in the UK, prostate MRI is more commonly used

that in other countries, so one would need to demonstrate applicability to less experienced urologists who may not be as used to prostate MRI. Though the study was UK based, the study group did contain some urologists with fairly limited prior exposure to prostate MRI. Improvement in performance was seen for urologists with the least experience in prostate MRI as well as for those with the greatest experience. Interesting, those with moderate prior experience did show improvement, though this was not statistically significant, which may be related to the small sample size.

This study has several strengths. First, the baseline and post-teaching MRIs were chosen at random to ensure that the difficultly of the scans was comparable between tests. Therefore, any differences in performance are more likely to be related to improvement of the participants than other confounding factors. Second, the reference standard used in the study was very detailed, meaning assessment of performance was likely to be reliable. Third, the tests were performed under test conditions, with the urologist blinded to pathology reports or radiology reports, thus ensuring a representative performance of the urologist's performance. Fourth, the course was delivered in a two-day format, practical and generalizable were it to be distributed more widely for urologists. Indeed, it has since been adopted as a European Association of Urology and the European School of Urology as the standardized syllabus for teaching this skill to urologists.

There are several limitations to our study. First, since not all patients underwent radical prostatectomy, assessment of agreement of extra-capsular extension with pathological findings was not possible. However, in order to assess the ability of participants to detect prostate cancer and avoid selection bias, it was necessary to have patients with and without cancer and not select men on basis of whether they underwent radical prostatectomy. Second, whether the benefits of this training persist is not known and it is not known whether participants could improve further with regular application of MRI reading in clinical practice or further training. Third, whether these improvements lead to improvements in patient care, for example better detection rates of significant cancer from MRI-targeted biopsy, is difficult to tangibly evaluate, though showing an improvement in MRI interpretation performance is the first step. Future research could focus on

assessing the performance of Urologist's over time to assess whether the skills gained persist and could focus on relating their performance to detection rates from MRI-targeted biopsy.

In conclusion, whilst we require expert radiologists to report prostate MRI, this study has demonstrated that prostate multi-parametric MRI interpretation by urologists can be improved by a short teaching course. This would support the provision of such training for urologists managing patients with prostate cancer and whom might be performing MRI-targeted biopsy and MRI-targeted treatments.

6.5 Statement of contribution

My personal contribution to this work is as follows:

- Study concept: My supervisor Mark Emberton and I came up with the study concept together
- Study design: I designed the study
- Acquisition of data: I collected the data from the 25 urologists who were course participants.
- Statistical analysis: I formulated the initial statistical analysis plan
- Analysis and interpretation of data: I was responsible for the analysis and interpretation of the data.

Other key contributions to this work:

- My supervisors Mark Emberton, Caroline Moore and Jan van der Meulen gave input into the study design.
- Alessandro Ambrosi finalised the statistical analysis plan and performed the statistical analysis.
- Francesco Giganti, Edwin Chau, Alex Kirkham, Shonit Punwani and Clare Allen assisted by providing their interpretation of the data for the publication, though none contributed directly to the writing of this thesis chapter

- I would like to thank the course faculty and administrative staff for their assistance in delivery of the course. This includes: Tufael Hussain, Edward Charnley, Sud Joy, Jason Peacocke, Vivek Mudera, Vasilis Stavrinides, Lina Carmona, Joana Neves, Chuanyu Gao, Yipeng Hu, Rachel Rodell, Ester Bonmati, Jon Piper, Pete Vicente, Clement Orzyck, Doug Pendse, Harbir Sidhu, Louise Dickinson, Edward Johnston, Greg Shaw, Anita Mitra.

6.6 Related Publication

Kasivisvanathan V, Ambrosi A, Giganti F, Chau E, Kirkham A, Punwani S, Allen C, Emberton M, Moore CM.

A Dedicated Prostate MRI Teaching Course Improves the Ability of the Urologist to Interpret Clinically Significant Prostate Cancer on Multiparametric MRI.

European Urology. 2019;75(1):203-4

Chapter 7 Final discussion and future directions

7.1 Emerging data from recently published studies

Several landmark studies have recently been published and their findings are important to discuss in the context of this thesis.

7.1.1 MRI-FIRST study

The MRI-FIRST study was a prospective multicentre paired cohort study carried out in 16 French centres [121]. They analysed 251 biopsy naïve men who underwent pre-biopsy multiparametric MRI with 1.5 Tesla or 3.0 Tesla magnet. These men underwent 12 core TRUS biopsy with the optional addition of 2 cores for hypoechoic areas seen on TRUS. They then underwent a targeted biopsy to MRI lesions scoring 3 or greater on the 1-5 Likert scale by a second operator. MRI-TB could be carried out with visual registration or software-assisted image fusion.

Key findings included that 19/251 (8%) patients had Gleason 7 or greater cancer identified only on MRI-TB. In addition, a targeted only approach would have avoided the diagnosis of 14% of men with clinically insignificant cancer (defined as Gleason 6 cancer with less than 6mm maximum cancer core length). For high grade cancer, Gleason 4+3 or greater, MRI-TB detected more cancer than TRUS biopsy (21% vs 15%, p = 0.0036). The authors concluded that MRI-TB has particular value in diagnosing high grade prostate cancer that can be missed by TRUS biopsy and in avoiding the diagnosis of clinically insignificant cancer. However, to maximise the diagnosis of clinically significant cancer they advocate combining both MRI-TB and systematic biopsy.

It is worth reflecting on the differences between the PRECISION trial and MRI-FIRST studies. Both support the use of pre-biopsy MRI and MRI-TB in the diagnosis of prostate cancer in biopsy naïve men, though PRECISION had a higher detection rate for MRI-TB than MRI-FIRST (38% vs 32%) and a greater benefit for MRI-TB over TRUS biopsy. A few key differences may explain these

findings. As the MRI-FIRST study was a paired cohort study and the MRI-TB was performed second it is possible that performance of the MRI-TB was influenced by the performance of the TRUS biopsy. Though a different operator carried out the MRI-TB, it is still possible that gland swelling, distortion of views on ultrasound imaging and needle track marks from the TRUS biopsy influenced the performance of the MRI-TB. Secondly, PRECISION allowed the biopsy of 3 suspicious areas, with up to 4 cores per suspicious area whereas MRI-FIRST allowed the biopsy of only 2 suspicious areas with up to 3 cores per suspicious area. Since the yield of significant cancer detection improves with more targeted cores [122], it is logical that cancer yields may be higher with more targeted cores. Finally, although the two populations studied are remarkably similar with respect to PSA and age, there is a difference in the proportion of men with abnormal digital rectal examination findings. In MRI-FIRST this was 31% versus 14-15% in PRECISION. This higher proportion of men with palpable abnormalities may explain why TRUS biopsy performed slightly better in the MRI-FIRST population than in the PRECISION population.

7.1.2 4M Study

A second landmark study in the field is the 4M study [94]. This was a prospective multicentre cohort study carried out in 4 Dutch centres, 3 of which were non-university centres. They analysed 643 men who underwent pre-biopsy multi-parametric MRI with a 3.0 Tesla magnet. All MRIs were reviewed centrally at the expert coordinating centre by two highly experienced radiologists. Men with a suspicious MRI, scoring 3 or greater on the PI-RADSv2 scoring system, underwent in-bore MRI-targeted biopsy with 2-4 cores per MRI suspicious area. All men also underwent 12-core TRUS biopsy. In men without an MRI lesion, they would undergo only TRUS biopsy.

Key findings in this study were that 309/626 (49%) of MRIs were scored as non-suspicious. MRI-TB detected 159/626 (25%) of men with clinically significant cancer defined as Gleason 3+4 or greater compared to 146/626 (23%) for TRUS biopsy. TRUS biopsy detected 3% of men with clinically significant cancer in the MRI-negative men. TRUS biopsy required 7512 biopsy cores compared to 849

cores for MRI-TB and also detected 155/626 (25%) of men with clinically insignificant cancer (Gleason 3+3) compared to 88/626 (14%) for MRI-TB. Translating these findings to clinical practice, MRI-TB would potentially allow 49% of men to avoid a biopsy, whilst detecting a similar amount of significant cancer to TRUS biopsy and greatly reducing the detection of insignificant cancer, thus supporting the role of MRI-TB in the prostate cancer diagnostic pathway. Additional learning points from this study include that when there is good quality control and double reading of the MRI by two highly experienced radiologists, that the ability to rule out suspicious areas on MRI can improve without necessarily compromising significant cancer detection.

7.1.3 Panebianco et al. negative MRI study

One of the limitations of the work in this thesis is that the medium to long-term outcomes of men who have a non-suspicious MRIs is not known. Though the cancer status of patients assessed at a single point of time is thoroughly assessed in this thesis and by others in the literature, little is known whether those men who test negative on the MRI go on to have clinically significant cancer identified over time.

Panebianco et al [93] looked at patients with negative MRI between 2010-2015 from their institution, with up to 7 years of follow up. Of 4952 patients undergoing MRI at their institution in the time frame, 1255 men had a negative MRI and were eligible for inclusion in the study. Of these 659 were biopsy naïve and 596 had a prior negative systematic biopsy. All patients were followed up with serial PSA, digital rectal examination and 8 monthly MRI scans. Biopsies were carried out when indicated by an MDT decision based on the follow up results.

After 48 months of follow up, the clinically significant cancer diagnosis-free probability was 94% for biopsy naïve men and 95% for men with prior negative systematic biopsy. These findings are encouraging as they support the concept that MRI is reliable at excluding significant cancer when men are followed up in the medium term. However, this study does have limitations. First, the institution involved is an expert centre in Prostate MRI so it cannot be assumed that an average centre can replicate these results. Second, the decisions for biopsy were

made by an MDT and every man was not biopsied. However, biopsying every man with a negative MRI regularly over time is not feasible or ethically sound, so the practice seen in this study is in line with routine clinical practice when an MRI-influenced diagnostic pathway is adopted. Thus, the data presented in this study is currently the best available to address this area of practice.

7.2 Limitations of MRI-TB and future directions

7.2.1 Standardisation of MRI reporting

When a change in practice occurs with the introduction and evaluation of a new technology, one of the limitations is quality control of the technology. In this case this involves ensuring that the standards of the MRI and MRI-TB at new centres adopting the technology are high.

With regards to the MRI, as can be seen from the PRECISION study in Table 5. 15, there is still some room for improvement in standardisation of MRI reporting. The inter-reader variability in prostate MRI interpretation is undesirably high [24, 95]. Whilst there is no consensus on which scoring system (Likert or PI-RADS) is the superior, both have been used in high profile studies [24, 49, 94, 121]. Changes to the PI-RADSv2 system have already been proposed [120, 123] and PI-RADSv3 is already in development. These changes may help to overcome some of these limitations.

7.2.2 Training of radiologists and urologists

With regards to training of radiologists and urologists to use the technology, this is an essential requirement when changing from a relatively straightforward diagnostic test of TRUS biopsy, carried out at most urological centres, to a more complex intervention of MRI and targeted biopsy. We have demonstrated that some of the skills required to interpret the prostate MRI are teachable, but national and international efforts need to be made in order to train clinicians to conduct the MRIs, interpret them, carry out targeted biopsies and use the information from this appropriately. This effort has begun, with the European Association of Urology endorsing MRI-prostate and MRI-targeted biopsy teaching

courses around Europe based on the course developed at our institution in Chapter 6. So far, 15 international courses have been delivered over the past 3 years and we have delivered a train-the-trainers course to allow Faculty across Europe to lead teaching efforts in their own countries.

7.2.3 Capacity of services to adopt MRI-targeted biopsy

With regards to capacity for carrying out MRI and MRI-TB, as MRI has been proposed here as the upfront test for men with raised PSA or abnormal digital rectal examination findings, much greater capacity would be required to meet the increased demand for prostate MRI. This will likely require MRI scanners in units dedicated only for prostate scanning, which requires a change in national and regional allocation of resources. In the UK, following publication of the PRECISION Trial, this process is already underway, which will be accelerated by the recent draft NICE guidelines, endorsing pre-biopsy MRI in men with suspected prostate cancer, before their first biopsy [124].

Part of the limitation in current capacity for multiparametric MRI is the requirement for all 3 of the key sequences to be carried out (i.e. T2-weighed, diffusion-weighted and contrast-enhanced imaging). The contrast enhanced imaging requires cannulation, intravenous contrast administration, staff trained to do this and a medical practitioner for safety reasons. This sequence also takes an additional 15-20 minutes contributing to a total scan time of 40 minutes. Avoiding the contrast sequences and carrying out a biparametric MRI (just T2-weighted and diffusion-weighted imaging) may halve the time it takes for an MRI to be carried out. Key studies have shown excellent detection rates of clinically significant cancer with biparametric MRI are possible [125] and thus if the capacity for prostate MRI can be doubled without compromising significant cancer detection rates, this may prove to be a reasonable solution. This will be the subject of a novel trial, which is in development by our institution, entitled Prostate Imaging using MRI +/- contrast Enhancement (PRIME).

7.2.4 Clinically significant cancer missed by MRI-TB

Another limitation in MRI-TB is that some significant cancer will be missed by the technique. However, no test is perfect and even a detailed 5mm transperineal template mapping biopsy will miss cancers, as demonstrated in PROMIS, where some cancers were missed by the template biopsy but detected by the TRUS biopsy. The solution is not just to take as many biopsies as possible because intensive biopsy strategies lead to a high rate of complications and are more resource intensive, which is not desirable to patients or healthcare services and is often not feasible in routine clinical practice [24, 25]. In patients undergoing transperineal template mapping biopsies, the PICTURE study reported acute urinary retention in 24% of patients and significant deterioration in erectile function, orgasmic function, sexual desire and intercourse [25]. Although this is the case, recent work on local anaesthetic transperineal biopsy approaches does seem like a promising compromise between resource use and sampling intensity [126]. However, robust outcomes of such diagnostic pathways are awaited, particularly with data showing the proportion of men diagnosed with clinically insignificant cancer.

A pragmatic option would be the approach taken in PRECISION, where the MRI was used to decide which men needed a biopsy. Those with a negative MRI could undergo PSA surveillance and avoid a biopsy and those with a positive MRI could undergo MRI-targeted biopsy. To minimise the amount of clinically significant cancer missed by the negative MRI, recent strategies have proposed using simple PSA derivatives such as PSA density. A PSA density lower than 0.15ng/ml/ml in the presence of a negative MRI has shown to improve the ability to rule out significant prostate cancer to around 95-100% [127]. Though this was not evaluated in PRECISION, it could be the subject of future research. Future research should also focus on reviewing cases where the MRI missed significant cancer, re-examining the MRI to see if there are particular MRI features that can be picked up in these men, re-examining the histopathology and identifying the reasons for misses by biopsy [128].

In men with a suspicious MRI undergoing MRI-TB, to minimise the amount of significant cancer missed, one option is to consider adding systematic biopsies to the targeted biopsies. The strategy would carry advantages of maximising the amount of clinically significant cancer detected, but would also mitigate the benefits of avoiding clinically insignificant cancer detection. Reports suggest that the amount of additional significant cancer identified is small [83, 92, 100, 129] and it is debateable whether this outweighs the benefit of avoiding the overdetection of insignificant cancer of the MRI-TB pathway.

7.2.5 Surgical planning

One of the putative limitations of an MRI-TB approach relates to surgical planning. During radical prostatectomy, nerve-sparing techniques have been developed to improve the functional outcomes of the procedure such as urinary continence and erectile function [130]. Though MRI itself does help to improve the appropriateness of decision making for nerve-sparing techniques [105], some surgeons value the certainty of histological information from both sides of the prostate to decide whether to spare the nerves on each side of the prostate.

In MRI-TB, where targeted biopsies are taken only from MRI-suspicious lesions, it is possible when there is only one MRI-suspicious lesion, that histological information on the presence or absence of cancer will only be present for one side of the prostate. If significant cancer is missed by the MRI on this side, this will affect the appropriateness of the decision for nerve sparing. However, others would argue that the biopsies of the MRI-negative part of the gland are systematic biopsies since there is no MRI-target and given the PROMIS study demonstrated that the negative predictive value of the MRI is greater than that of the systematic biopsy, it would not make sense to carry out systematic biopsy if we know the MRI is negative [24]. Further, we know from Section 1.6 about the errors associated with systematic biopsy, particularly the over-diagnosis of insignificant cancer which can lead to unnecessary treatment and higher morbidity from a greater number of biopsies.

7.2.6 Future research: patient preferences for diagnostic tests

Future research should focus on evaluation of patient preferences for the optimal balance of diagnosing clinically significant cancer and avoiding the diagnosis of clinically insignificant cancer and this should inform our decision-making process on the approach we take. Certainly, if we consider the currently available data on long-term outcomes from treating a large cohort of men with primarily low-risk localised prostate cancer, the benefits of radical treatment are low as the mortality risk in these men is also low [33]. The harms caused to these patients from treatment are significant [85], so perhaps a change in emphasis by selecting the right men to treat may offer potential for greater benefit of treatment.

Understanding what is important to patients when they are presented with the possibilities of what might happen when significant and insignificant are diagnosed, may help to inform what diagnostic approach we take for that patient. For example, one man may value certainty of diagnosis with a highly detailed test sampling the entire prostate, even if the side effects of the test and the risk of being over diagnosed with insignificant cancer and being over treated are high. Another man, however, may value only going through a biopsy test if the risks of significant cancer being identified are high and may be willing to accept the small risk of missing some significant cancer, providing that the majority of significant cancer is identified and if the test that is carried out carries a low morbidity and has a low risk of identifying insignificant cancer.

7.2.7 Future research: long-term outcomes

Future research should focus on evaluating the long-term oncological outcomes of men risk-stratified with MRI and MRI-TB from the outset. Much of the current literature on the traditional diagnostic pathway for men with prostate cancer is based on men undergoing TRUS-biopsy without a prior MRI. Long-term survival outcomes for men undergoing observation, active surveillance or radical treatment have been published in the PIVOT and PROTECT studies [33, 131]. These observations have helped influence how clinicians select men for treatment, with men who have low risk disease having limited benefit for radical treatment and radical treatment having more benefit in men with at least 10 years

of life expectancy remaining. However, as this work was done prior to the routine use of pre-biopsy MRI, it is not known how pre-biopsy MRI and an MRI-influenced decision-making process, influences these outcomes. Our institution has more than a decade worth of data for men risk-stratified with pre-biopsy MRI and work has begun to evaluate whether survival varies in men with different levels of MRI suspicion and whether survival is different when cancer is diagnosed with MRI-TB rather than the traditional pathways. It would be important to demonstrate a difference in survival outcomes in men with a suspicious MRI compared to those with a non-suspicious MRI and would be interesting to evaluate whether MRI-TB influences the relative benefit of different treatment options in these men.

7.2.8 Future research: MRI-screening

A further area of future research would involve changing the paradigm for the diagnosis of prostate cancer completely. Currently men are identified at being of clinical risk of prostate cancer primarily based on raised PSA or abnormal digital rectal examination. The current place for a prostate MRI is in men who have already had these tests. Given the limitations of a PSA-based pathway [30-32], another option would be to carry out an MRI upfront in healthy men, prior to or in place of a PSA test. Given the ability of Prostate MRI and MRI-TB to identify men with clinically significant cancer, if its performance characteristics in men when carried out at this stage are good then it may have a role as an upfront diagnostic tool in prostate cancer evaluation. This area of work is currently being investigated in a Medical Research Council-funded study Re-IMAGINE, led by our research group. This is an extremely controversial area of medical practice with significant cost, resource and clinical implications. It will explore a number of downstream effects of introducing MRI at an earlier stage of the pathway.

7.3 Discussion and conclusion

The body of work in this thesis effectively portrays the journey that MRI-TB has taken in clinical practice over the past few years in this rapidly moving field. The work included in the thesis has helped the technique develop from being a diagnostic technique under investigation [53], to one being considered in select

group of patients [75], to one proposed in national and international guidelines as the standard of care for diagnosing men with suspected prostate cancer [124, 132].

We have learnt from a single institution study (Chapter 2) that MRI-TB had the potential to detect a similar amount of clinically significant as detailed transperineal prostate biopsies whilst avoiding the overdetection of clinically insignificant cancer. Despite systematic review evidence supporting the benefits of an MRI-TB approach over a TRUS biopsy approach, clinical practice was not changing. We learnt in Chapter 3 that studies evaluating MRI-TB were poorly reported which may explain the lack of drive to consider a change of practice and we established new reporting standards amongst an expert group. Within this group and using these reporting standards, we designed a study to compare MRI-TB to the standard of care, TRUS biopsy, to evaluate the potential of multiparametric MRI±TB as a replacement test for TRUS biopsy (Chapter 4). We carried out this multicentre randomized trial, PRECISION, and provided level 1 evidence that MRI±TB was superior to TRUS biopsy in the detection of clinically significant cancer, in avoiding the detection of clinically insignificant cancer and in being more efficient, requiring fewer biopsy cores in its application (Chapter 5). Finally, I considered some of the practical aspects of adopting this technology, demonstrating that teaching courses can improve the performance of clinicians in using the technology (Chapter 6).

This work has supported a change in guideline recommendations for prostate cancer diagnosis in the European Association of the Urology (EAU) and the National Institute for Health and Care Excellence (NICE) UK prostate cancer guidelines. The 2019 EAU prostate cancer guidelines [133] and the provisional 2019 NICE prostate cancer diagnosis and management guidelines [134], for the first time, support pre-biopsy MRI and the addition of MRI-targeted biopsy in biopsy naïve men and in men with prior negative TRUS biopsy who have suspicion of prostate cancer. Both guidelines, for the first time, support the possibility of avoiding biopsy in men with non-suspicious MRIs who have low risk of clinically significant cancer, after an informed discussion with the patient.

These recommendations are a significant change for patients with clinical suspicion of prostate cancer.

In conclusion, I have demonstrated that using multiparametric MRI in men with clinical suspicion of prostate cancer followed by MRI-TB in men with suspicious lesions on MRI is a valid alternative to rival the existing standard of care of TRUS biopsy. It carries advantages of better identifying men with aggressive disease who are likely to benefit from treatment and avoiding the diagnosis of men with disease less likely to benefit from treatment. It is a more efficient test, requiring fewer biopsies and allowing more men to avoid the discomfort and risks of a biopsy altogether. Though challenges remain, notably in adoption of the technology on a wider scale, ensuring high quality of multiparametric MRI and training of clinicians in use of the technology, these challenges are likely surmountable and I look forward to the long-term outcomes of men risk-stratified with this approach.

Chapter 8 Appendices

A. Research Fellowships and Grants

1. National Institute for Health and Research Doctoral Fellowship - £355,000, 2014-2017. Supervisors: Caroline Moore, Mark Emberton, Jan van der Meulen. This was awarded to me by competitive national application for the purpose of funding my salary and partial costs of my PhD work.

2. European Association of Urology Research Foundation – €36,200, 2015-2019. Chief Investigators: Caroline Moore, Mark Emberton. This was awarded to me by competitive international application for the purpose of funding trial costs associated with the PRECISION trial.

3. European Association of Urology, Prostate Cancer UK, CIVCO, IPSEN, SmartTarget, London Cancer, Hitachi, Kyowa Kirin - £44,341.
   Prostate Cancer UK funding was awarded by competitive national application. Other funding was on request for sponsorship. All funding was for delivery of the MRI Teaching Course over the course of 3 years.

4. Movember Foundation, Ontario Institute for Cancer Research and Prostate Cancer Canada – C$3,000,000.
   Awarded to Chief Investigator Laurence Klotz for the PRECISE Study. I was named as Collaborator on the grant. The PRECISE Study was modelled on the PRECISION study and is a Canadian version of it.

B. Awards and Prizes

1. **British Medical Journal** 2019 UK Research paper of the year across all medical specialities, for PRECISION study.

2. **European Association of Urology** Prostate Cancer Research Award for best prostate cancer research paper published in 2018 for PRECISION study.

3. British Association of Urological Surgeon's 2019 **John Anderson Award** for outstanding and inspirational contribution to the Speciality of Urology. This award in part recognised my work on the PRECISION trial and work in developing MRI education in Europe.

4. **Evening Standard's Award** for one of London's Most Influential People in Health in 2018. Unsolicited award for my work in Prostate Cancer Research.

5. **UCL Provost Excellence 2018 Award.** Awarded to me for exceptional contribution to the University, with respect to Commitment to excellence, Leadership, Innovation and creativity related to work associated with my PhD.

6. **Runner up**, Prostate Cancer Foundation Provocative 25 Research Enterprise Award 2018, for outstanding research, for the PRECISION Study.

7. **American Urology Association 2017 Visiting Scholarship** awarded for excellence in my research and potential to become a future leader in Urology. Attended University of Southern California, Institute of Urology for this award.

8. **University College London Hospital Celebrating Excellence Award 2016.** I was one of the team at University College Hospital London awarded this award for Contribution to World Class Research.

9. **UK Healthcare Leaders Health Services Journal Award for Acute Sector Innovation 2015.** I was one of the team at University College Hospital London awarded this award for Prostate Cancer Care Innovation.

10. **British Medical Journal UK Team of the Year for Innovation Award 2015.** I was one of the team at University College Hospital London awarded this award for Prostate Cancer care Innovation.

11. **NIHR Cancer Research Excellence in Surgical Trials Commendation in 2015.** I was one of the team at University College Hospital London awarded this award for excellent contribution to the clinical trials portfolio.

12. **Best Paper of 2014 Award** at European Association of Urology, Section of Oncological Urology 2014, Prague, for START Consortium Guidelines on Standard for Reporting MRI-Targeted biopsy studies (Chapter 3).

C. *Full list of related Journal Publications*

1. Kasivisvanathan V, Rannikko AS, Borghi M, Panebianco V, Mynderse LA, Vaarala MH, et al. MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. N Engl J Med. 2018;378:1767-77

2. Kasivisvanathan V, Jichi F, Klotz L, Villers A, Taneja SS, Punwani S, et al. A multicentre randomised controlled trial assessing whether MRI-targeted biopsy is non-inferior to standard transrectal ultrasound guided biopsy for the diagnosis of clinically significant prostate cancer in men without prior biopsy: a study protocol. BMJ Open. 2017;7:e017863.

3. Kasivisvanathan V, Ambrosi A, Giganti F, Chau E, Kirkham A, Punwani S, et al. A Dedicated Prostate MRI Teaching Course Improves the Ability of the Urologist to Interpret Clinically Significant Prostate Cancer on Multiparametric MRI. European Urology. 2019;75:203-4.

4. Kasivisvanathan V, Dufour R, Moore CM, Ahmed HU, Abd-Alazeez M, Charman SC, et al. Transperineal magnetic resonance image targeted prostate biopsy versus transperineal template prostate biopsy in the detection of clinically significant prostate cancer. J Urol. 2013;189:860-6.

5. Moore CM*, Kasivisvanathan V*, Eggener S, Emberton M, Futterer JJ, Gill IS, et al. Standards of Reporting for MRI-targeted Biopsy Studies (START) of the Prostate: Recommendations from an International Working Group. Eur Urol. 2013;64:544-52. (*Joint 1st author)

6. Hu Y, Kasivisvanathan V, Simmons LAM, Clarkson MJ, Thompson SA, Shah TT, et al. Development and Phantom Validation of a 3-D-Ultrasound-Guided System for Targeting MRI-Visible Lesions During Transrectal Prostate Biopsy. IEEE transactions on bio-medical engineering. 2017;64:946-58.

7. Kasivisvanathan V, Emberton M, Moore CM. *Don't Let the Perfect Be the Enemy of the Good: Time to Embrace Magnetic Resonance Imaging Before First Prostate Biopsy*. Eur Urol. 2018 Oct;74(4):411-412. doi: 10.1016/j.eururo.2018.06.012.

8. Rivas JG, Giganti F, Álvarez-Maestro M, Freire MJ, Kasivisvanathan V, Martinez-Piñero L, Emberton M. *Prostate Indeterminate Lesions on Magnetic Resonance Imaging-Biopsy Versus Surveillance: A Literature Review*. Eur Urol Focus. 2018 Mar 7. pii: S2405-4569(18)30074-9. doi: 10.1016/j.euf.2018.02.012.

9. Rhudd A, McDonald J, Emberton M, Kasivisvanathan V. *The role of the multiparametric MRI in the diagnosis of prostate cancer in biopsy-naïve men.* Curr Opin Urol. 2017 Sep. ;27(5):488-494. doi: 10.1097/MOU.0000000000000415.

10. van der Sar* E, Kasivisvanathan V*, Brizmohun M, Freeman A, Punwani S, Hamoudi R, Emberton M. *Management of Radiologically Indeterminate Magnetic Resonance Imaging Signals in Men at Risk of Prostate Cancer.* Eur Urol Focus; 2017 Apr 19. http://dx.doi.org/10.1016/j.euf.2017.03.016. (*Joint 1st author*)

11. Chau EM, Arya M, Petrides N, Aldin Z, McKenzie J, Emberton M, Virdi J, Ahmed H.U, Kasivisvanathan V. Performance characteristics of multiparametric-MRI at a non-academic hospital using transperineal template mapping biopsy as a reference standard. International Journal of Surgery Open. 2018;10:66-71

D. Related Research Presentations

All given as the presenting author, unless otherwise specified:

1. PRECISION and PROMIS trials. Invited oral presentation, 16th March 2019, European Association of Urology 2019 Meeting, Barcelona.

2. "MRI-targeted biopsy is enough". Invited oral plenary presentation, 17th March 2019, European Association of Urology 2019 Meeting, Barcelona.

3. Best of BAUS, breaking news session: the PRECISION Trial. Oral presentation, British Association of Urological Surgeons 2018 Conference, Liverpool, 27th June 2018.

4. A multi-centre randomised controlled trial assessing whether MRI-targeted biopsy is non-inferior to standard trans-rectal ultrasound guided biopsy for the diagnosis of clinically significant prostate cancer in men without prior biopsy - the PRECISION study: PRostate Evaluation for Clinically Important disease, Sampling using Image-guidance Or Not? (NCT02380027). Poster and oral presentation, American Urology Association 2018 Conference, San Fransisco, 21st May 2018. (Presented by Chief Investigator Caroline Moore)

5. Prostate evaluation for clinically important disease: Sampling using image-guidance or not? (The PRECISION study, NCT02380027). Invited oral plenary presentation, 19th March 2018, European Association of Urology 2018 Meeting, Copenhagen.

6. A training course for the Urologist improves their ability to interpret clinically significant prostate cancer on multiparametric MRI. Oral and poster presentation, 14th May 2017, American Urology Association 2017 Conference, Boston, USA.

7. The PRECISION Study: a European Association of Urology Research Foundation project. Oral presentation. Invited talk. European Association of Urology 2017 Meeting, London, 24th-28th April 2017.

8. Progress and future direction of the PRECISION Study. Oral presentation. European Association of Urology 2017 Meeting, London, 24th-28th April 2017.

E. Additional study during thesis

1. Postgraduate Certificate in Clinical Trials (Distinction), University of London, August 2015 - November 2017.

2. Introduction to Health Economics MSc Module, University of London, August 2014 - November 2015.

3. Advanced Economic analysis for Health Policy MSc Module, University of London, August 2014 - November 2015.

4. Analytical Models for Decision Making MSc Module, University of London, August 2014 - November 2015.

5. Masters in Epidemiology, University of London, University of London, August 2011 - November 2014.

References

[1] Ferlay J, Ervik M, Lam F, et al. Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.fr/today, accessed on 6th November 2018. 2018.

[2] Cancer Research UK Prostate cancer mortality statistics. Available from: http://www.cancerresearchuk.org/cancer-info/cancerstats/types/prostate/mortality/uk-prostate-cancer-mortality-statistics. Accessed on 6th November 2018.

[3] Taitt HE. Global Trends and Prostate Cancer: A Review of Incidence, Detection, and Mortality as Influenced by Race, Ethnicity, and Geographic Location. American journal of men's health. 2018;12:1807-23.

[4] Bratt O. Hereditary Prostate Cancer: Clinical Aspects. The Journal of Urology. 2002;168:906-13.

[5] Castro E, Eeles R. The role of BRCA1 and BRCA2 in prostate cancer. Asian journal of andrology. 2012;14:409-14.

[6] Karlsson R, Aly M, Clements M, et al. A population-based assessment of germline HOXB13 G84E mutation and prostate cancer risk. Eur Urol. 2014;65:169-76.

[7] Arnold M, Razum O, Coebergh JW. Cancer risk diversity in non-western migrants to Europe: An overview of the literature. European journal of cancer. 2010;46:2647-59.

[8] Humphrey PA. Histopathology of Prostate Cancer. Cold Spring Harbor perspectives in medicine. 2017;7.

[9] Gleason DF. Classification of prostatic carcinomas. Cancer chemotherapy reports. 1966;50:125-8.

[10] Epstein JI, Allsbrook WC, Jr., Amin MB, Egevad LL, Committee IG. The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. The American journal of surgical pathology. 2005;29:1228-42.

[11] Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR, Humphrey PA. The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma: Definition of Grading

Patterns and Proposal for a New Grading System. The American journal of surgical pathology. 2016;40:244-52.
[12] Stamey TA, Kabalin JN, McNeal JE, et al. Prostate specific antigen in the diagnosis and treatment of adenocarcinoma of the prostate. II. Radical prostatectomy treated patients. J Urol. 1989;141:1076-83.
[13] Hodge KK, McNeal JE, Stamey TA. Ultrasound guided transrectal core biopsies of the palpably abnormal prostate. J Urol. 1989;142:66-70.
[14] Presti JC, Jr., O'Dowd GJ, Miller MC, Mattu R, Veltri RW. Extended peripheral zone biopsy schemes increase cancer detection rates and minimize variance in prostate specific antigen and age related cancer rates: results of a community multi-practice study. J Urol. 2003;169:125-9.
[15] Bauer JJ, Zeng J, Weir J, et al. Three-dimensional computer-simulated prostate models: lateral prostate biopsies increase the detection rate of prostate cancer. Urology. 1999;53:961-7.
[16] Guichard G, Larre S, Gallina A, et al. Extended 21-sample needle biopsy protocol for diagnosis of prostate cancer in 1000 consecutive patients. Eur Urol. 2007;52:430-5.
[17] Epstein JI, Zelefsky MJ, Sjoberg DD, et al. A Contemporary Prostate Cancer Grading System: A Validated Alternative to the Gleason Score. European Urology. 2016;69:428-35.
[18] Salomon L, Levrel O, Anastasiadis A, et al. Prognostic significance of tumor volume after radical prostatectomy: a multivariate analysis of pathological prognostic factors. European urology. 2003;43:39.
[19] Hu Y, Ahmed HU, Carter T, et al. A biopsy simulation study to assess the accuracy of several transrectal ultrasonography (TRUS)-biopsy strategies compared with template prostate mapping biopsies in patients who have undergone radical prostatectomy. BJU Int. 2012;110:812-20.
[20] Serefoglu EC, Altinova S, Ugras NS, Akincioglu E, Asil E, Balbay MD. How reliable is 12-core prostate biopsy procedure in the detection of prostate cancer? Canadian Urological Association journal = Journal de l'Association des urologues du Canada. 2013;7:E293-E8.
[21] Loeb S, Vellekoop A, Ahmed HU, et al. Systematic Review of Complications of Prostate Biopsy. Eur Urol. 2013.

[22] Holm HH, Gammelgaard J. Ultrasonically guided precise needle placement in the prostate and the seminal vesicles. J Urol. 1981;125:385-7.
[23] Onik G, Miessau M, Bostwick DG. Three-dimensional prostate mapping biopsy has a potentially significant impact on prostate cancer management. J Clin Oncol. 2009;27:4321-6.
[24] Ahmed HU, El-Shater Bosaily A, Brown LC, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet. 2017;389:815-22.
[25] Miah S, Eldred-Evans D, Simmons LAM, et al. Patient Reported Outcome Measures for Transperineal Template Prostate Mapping Biopsies in the PICTURE Study. The Journal of Urology. 2018.
[26] Borghesi M, Ahmed H, Nam R, et al. Complications After Systematic, Random, and Image-guided Prostate Biopsy. European Urology. 2017;71:353-65.
[27] Kuru TH, Wadhwa K, Chang RT, et al. Definitions of terms, processes and a minimum dataset for transperineal prostate biopsies: a standardization approach of the Ginsburg Study Group for Enhanced Prostate Diagnostics. BJU Int. 2013;112:568-77.
[28] Bass EJ, Donaldson IA, Freeman A, et al. Magnetic resonance imaging targeted transperineal prostate biopsy: a local anaesthetic approach. Prostate Cancer Prostatic Dis. 2017;20:311-7.
[29] Etzioni R, Penson DF, Legler JM, et al. Overdiagnosis Due to Prostate-Specific Antigen Screening: Lessons From U.S. Prostate Cancer Incidence Trends. JNCI: Journal of the National Cancer Institute. 2002;94:981-90.
[30] Andriole GL, Crawford ED, Grubb RL, 3rd, et al. Prostate cancer screening in the randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial: mortality results after 13 years of follow-up. J Natl Cancer Inst. 2012;104:125-32.
[31] Schröder FH, Hugosson J, Roobol MJ, et al. Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. Lancet (London, England). 2014;384:2027-35.
[32] Martin RM, Donovan JL, Turner EL, et al. Effect of a Low-Intensity PSA-Based Screening Intervention on Prostate Cancer Mortality: The CAP Randomized Clinical Trial. Jama. 2018;319:883-95.

[33] Hamdy FC, Donovan JL, Lane JA, et al. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. N Engl J Med. 2016;375:1415-24.
[34] Wilt TJ, Brawer MK, Jones KM, et al. Radical prostatectomy versus observation for localized prostate cancer. N Engl J Med. 2012;367:203-13.
[35] Barocas DA, Alvarez J, Resnick MJ, et al. Association between radiation therapy, surgery, or observation for localized prostate cancer and patient-reported outcomes after 3 years. JAMA. 2017;317:1126-40.
[36] Catalona WJ, Partin AW, Slawin KM, et al. Use of the percentage of free prostate-specific antigen to enhance differentiation of prostate cancer from benign prostatic disease: a prospective multicenter clinical trial. Jama. 1998;279:1542-7.
[37] Roddam AW, Duffy MJ, Hamdy FC, et al. Use of prostate-specific antigen (PSA) isoforms for the detection of prostate cancer in men with a PSA level of 2-10 ng/ml: systematic review and meta-analysis. Eur Urol. 2005;48:386-99; discussion 98-9.
[38] Carter HB, Pearson JD, Metter EJ, et al. Longitudinal evaluation of prostate-specific antigen levels in men with and without prostate disease. Jama. 1992;267:2215-20.
[39] Jue JS, Barboza MP, Prakash NS, et al. Re-examining Prostate-specific Antigen (PSA) Density: Defining the Optimal PSA Range and Patients for Using PSA Density to Predict Prostate Cancer Using Extended Template Biopsy. Urology. 2017;105:123-8.
[40] Lazzeri M, Haese A, de la Taille A, et al. Serum Isoform [−2]proPSA Derivatives Significantly Improve Prediction of Prostate Cancer at Initial Biopsy in a Total PSA Range of 2–10 ng/ml: A Multicentric European Study. European Urology. 2013;63:986-94.
[41] Vickers A, Cronin A, Roobol M, et al. Reducing unnecessary biopsy during prostate cancer screening using a four-kallikrein panel: an independent replication. J Clin Oncol. 2010;28:2493-8.
[42] Van Neste L, Hendriks RJ, Dijkstra S, et al. Detection of High-grade Prostate Cancer Using a Urinary Molecular Biomarker-Based Risk Score. Eur Urol. 2016;70:740-8.

[43] Nakanishi H, Groskopf J, Fritsche HA, et al. PCA3 molecular urine assay correlates with prostate cancer tumor volume: implication in selecting candidates for active surveillance. J Urol. 2008;179:1804-9; discussion 9-10.
[44] Ahmed HU, Kirkham A, Arya M, et al. Is it time to consider a role for MRI before prostate biopsy? Nat Rev Clin Oncol. 2009;6:197-206.
[45] Tanimoto A, Nakashima J, Kohno H, Shinmoto H, Kuribayashi S. Prostate cancer screening: the clinical value of diffusion-weighted imaging and dynamic MR imaging in combination with T2-weighted imaging. J Magn Reson Imaging. 2007;25:146-52.
[46] Dickinson L, Ahmed HU, Allen C, et al. Magnetic resonance imaging for the detection, localisation, and characterisation of prostate cancer: recommendations from a European consensus meeting. Eur Urol. 2011;59:477-94.
[47] Barentsz JO, Richenberg J, Clements R, et al. ESUR prostate MR guidelines 2012. Eur Radiol. 2012;22:746-57.
[48] Weinreb JC, Barentsz JO, Choyke PL, et al. PI-RADS Prostate Imaging - Reporting and Data System: 2015, Version 2. Eur Urol. 2016;69:16-40.
[49] Kasivisvanathan V, Rannikko AS, Borghi M, et al. MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. N Engl J Med. 2018;378:1767-77.
[50] Bossuyt PM, Irwig L, Craig J, Glasziou P. Comparative accuracy: assessing new tests against existing diagnostic pathways. BMJ. 2006;332:1089-92.
[51] Moore CM, Robertson NL, Arsanious N, et al. Image-guided prostate biopsy using magnetic resonance imaging-derived targets: a systematic review. Eur Urol. 2013;63:125-40.
[52] Haffner J, Lemaitre L, Puech P, et al. Role of magnetic resonance imaging before initial biopsy: comparison of magnetic resonance imaging-targeted and systematic biopsy for significant prostate cancer detection. BJU Int. 2011;108:E171-8.
[53] Kasivisvanathan V, Dufour R, Moore CM, et al. Transperineal magnetic resonance image targeted prostate biopsy versus transperineal template prostate biopsy in the detection of clinically significant prostate cancer. J Urol. 2013;189:860-6.
[54] Ahmed HU, Hu Y, Carter T, et al. Characterizing clinically significant prostate cancer using template prostate mapping biopsy. J Urol. 2011;186:458-64.

[55] Hutchinson R, Lotan Y. Cost consideration in utilization of multiparametric magnetic resonance imaging in prostate cancer. Translational andrology and urology. 2017;6:345-54.

[56] Hamid S, Donaldson IA, Hu Y, et al. The SmartTarget Biopsy Trial: A Prospective, Within-person Randomised, Blinded Trial Comparing the Accuracy of Visual-registration and Magnetic Resonance Imaging/Ultrasound Image-fusion Targeted Biopsies for Prostate Cancer Risk Stratification. European Urology.

[57] Miyagawa T, Ishikawa S, Kimura T, et al. Real-time Virtual Sonography for navigation during targeted prostate biopsy using magnetic resonance imaging data. Int J Urol. 2010;17:855-60.

[58] Keegan KA, Dall'Era MA, Durbin-Johnson B, Evans CP. Active surveillance for prostate cancer compared with immediate treatment: an economic analysis. Cancer. 2012;118:3512-8.

[59] Schoots IG, Roobol MJ, Nieboer D, Bangma CH, Steyerberg EW, Hunink MG. Magnetic resonance imaging-targeted biopsy may enhance the diagnostic accuracy of significant prostate cancer detection compared to standard transrectal ultrasound-guided biopsy: a systematic review and meta-analysis. Eur Urol. 2015;68:438-50.

[60] Hadaschik BA, Kuru TH, Tulea C, et al. A novel stereotactic prostate biopsy system integrating pre-interventional magnetic resonance imaging and live ultrasound fusion. J Urol. 2011;186:2214-20.

[61] van Hove A, Savoie PH, Maurin C, et al. Comparison of image-guided targeted biopsies versus systematic randomized biopsies in the detection of prostate cancer: a systematic literature review of well-designed studies. World J Urol. 2014;32:847-58.

[62] Kuru TH, Roethke MC, Seidenader J, et al. Critical evaluation of magnetic resonance imaging targeted, transrectal ultrasound guided transperineal fusion biopsy for detection of prostate cancer. J Urol. 2013;190:1380-6.

[63] Moore CM, Kasivisvanathan V, Eggener S, et al. Standards of Reporting for MRI-targeted Biopsy Studies (START) of the Prostate: Recommendations from an International Working Group. Eur Urol. 2013;64:544-52.

[64] Reporting Guidelines for the Enhacing the QUAlity and transparency Of health Research (EQUATOR) Network. available from https://www.equator-network.org/reporting-guidelines/. Accessed on: 2nd January 2019.

[65] Bossuyt PM, Reitsma JB, Bruns DE, et al. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Clin Radiol. 2003;58:575-80.

[66] Fitch K, Bernstein SJ, Aguilar MD, et al. The RAND/UCLA Appropriateness Method User's Manual. Santa Monica, CA: RAND corporation; 2001.

[67] Manenti G, Nezzo M, Chegai F, Vasili E, Bonanno E, Simonetti G. DWI of Prostate Cancer: Optimal b-Value in Clinical Practice. Prostate cancer. 2014;2014:868269-.

[68] Rosenkrantz AB, Kim S, Lim RP, et al. Prostate cancer localization using multiparametric MR imaging: comparison of Prostate Imaging Reporting and Data System (PI-RADS) and Likert scales. Radiology. 2013;269:482-92.

[69] Rosenkrantz AB, Lim RP, Haghighi M, Somberg MB, Babb JS, Taneja SS. Comparison of interreader reproducibility of the prostate imaging reporting and data system and likert scales for evaluation of multiparametric prostate MRI. AJR Am J Roentgenol. 2013;201:W612-8.

[70] Goto Y, Ohori M, Arakawa A, Kattan MW, Wheeler TM, Scardino PT. Distinguishing clinically important from unimportant prostate cancers before treatment: value of systematic biopsies. J Urol. 1996;156:1059-63.

[71] Wolters T, Roobol MJ, van Leeuwen PJ, et al. A critical analysis of the tumor volume threshold for clinically insignificant prostate cancer using a data set of a randomized screening trial. J Urol. 2011;185:121-5.

[72] Epstein JI, Walsh PC, Carmichael M, Brendler CB. Pathologic and clinical findings to predict tumor extent of nonpalpable (stage T1c) prostate cancer. JAMA. 1994;271:368-74.

[73] Robertson NL, Hu Y, Ahmed HU, Freeman A, Barratt D, Emberton M. Prostate cancer risk inflation as a consequence of image-targeted biopsy of the prostate: a computer simulation study. Eur Urol. 2014;65:628-34.

[74] Kasivisvanathan V, Jichi F, Klotz L, et al. A multicentre randomised controlled trial assessing whether MRI-targeted biopsy is non-inferior to standard transrectal ultrasound guided biopsy for the diagnosis of clinically significant prostate cancer in men without prior biopsy: a study protocol. BMJ Open. 2017;7:e017863.

[75] Heidenreich A, Bastian PJ, Bellmunt J, et al. EAU guidelines on prostate cancer. part 1: screening, diagnosis, and local treatment with curative intent-update 2013. Eur Urol. 2014;65:124-37.
[76] EuroQol G. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy. 1990;16:199-208.
[77] Rosario DJ, Lane JA, Metcalfe C, et al. Short term outcomes of prostate biopsy in men tested for cancer by prostate specific antigen: prospective evaluation within ProtecT study. BMJ. 2012;344:d7894.
[78] Loudon K, Treweek S, Sullivan F, Donnan P, Thorpe KE, Zwarenstein M. The PRECIS-2 tool: designing trials that are fit for purpose. BMJ. 2015;350:h2147.
[79] NHS Reference Costs 2015-2016, Department of Health. Available from https://improvement.nhs.uk/resources/reference-costs/. Accessed on 2nd January 2019.
[80] National Collaborating Centre for Cancer 2014 Full Guideline, commissioned by National Institute for Health and Care Excellence. Available from: https://www.nice.org.uk/guidance/cg175/evidence/full-guideline-191710765. Accessed on 2nd January 2019.
[81] Curtis L, Burns A. Unit costs of Health and Social Care 2016 published by the Personal Social Services Research Unit. Accessible from: https://www.pssru.ac.uk/pub/uc/uc2016/full.pdf?uc=2016-full. Accessed on 2nd January 2019.
[82] Porpiglia F, Manfredi M, Mele F, et al. Diagnostic Pathway with Multiparametric Magnetic Resonance Imaging Versus Standard Pathway: Results from a Randomized Prospective Study in Biopsy-naive Patients with Suspected Prostate Cancer. Eur Urol. 2017;72:282-8.
[83] Baco E, Rud E, Eri LM, et al. A Randomized Controlled Trial To Assess and Compare the Outcomes of Two-core Prostate Biopsy Guided by Fused Magnetic Resonance and Transrectal Ultrasound Images and Traditional 12-core Systematic Biopsy. Eur Urol. 2016;69:149-56.
[84] Tonttila PP, Lantto J, Paakko E, et al. Prebiopsy Multiparametric Magnetic Resonance Imaging for Prostate Cancer Diagnosis in Biopsy-naive Men with Suspected Prostate Cancer Based on Elevated Prostate-specific Antigen Values:

Results from a Randomized Prospective Blinded Controlled Trial. Eur Urol. 2016;69:419-25.
[85] Donovan JL, Hamdy FC, Lane JA, et al. Patient-Reported Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer. N Engl J Med. 2016;375:1425-37.
[86] Resnick MJ, Koyama T, Fan KH, et al. Long-term functional outcomes after treatment for localized prostate cancer. N Engl J Med. 2013;368:436-45.
[87] Bergman J, Litwin MS. Quality of life in men undergoing active surveillance for localized prostate cancer. Journal of the National Cancer Institute Monographs. 2012;2012:242-9.
[88] Faria R, Soares MO, Spackman E, et al. Optimising the Diagnosis of Prostate Cancer in the Era of Multiparametric Magnetic Resonance Imaging: A Cost-effectiveness Analysis Based on the Prostate MR Imaging Study (PROMIS). Eur Urol. 2018;73:23-30.
[89] de Rooij M, Crienen S, Witjes JA, Barentsz JO, Rovers MM, Grutters JP. Cost-effectiveness of magnetic resonance (MR) imaging and MR-guided targeted biopsy versus systematic transrectal ultrasound-guided biopsy in diagnosing prostate cancer: a modelling study from a health care perspective. Eur Urol. 2014;66:430-6.
[90] Cerantola Y, Dragomir A, Tanguay S, Bladou F, Aprikian A, Kassouf W. Cost-effectiveness of multiparametric magnetic resonance imaging and targeted biopsy in diagnosing prostate cancer. Urol Oncol. 2016;34:119 e1-9.
[91] Barnett CL, Davenport MS, Montgomery JS, Wei JT, Montie JE, Denton BT. Cost-effectiveness of magnetic resonance imaging and targeted fusion biopsy for early detection of prostate cancer. BJU Int. 2018;122:50-8.
[92] Panebianco V, Barchetti F, Sciarra A, et al. Multiparametric magnetic resonance imaging vs. standard care in men being evaluated for prostate cancer: A randomized study. Urol Oncol. 2015;33:17 e1-7.
[93] Panebianco V, Barchetti G, Simone G, et al. Negative Multiparametric Magnetic Resonance Imaging for Prostate Cancer: What's Next? Eur Urol. 2018;74:48-54.
[94] van der Leest M, Cornel E, Israël B, et al. Head-to-head Comparison of Transrectal Ultrasound-guided Prostate Biopsy Versus Multiparametric Prostate Resonance Imaging with Subsequent Magnetic Resonance-guided Biopsy in

Biopsy-naïve Men with Elevated Prostate-specific Antigen: A Large Prospective Multicenter Clinical Study. European Urology. 2018.
[95] Rosenkrantz AB, Ginocchio LA, Cornfeld D, et al. Interobserver Reproducibility of the PI-RADS Version 2 Lexicon: A Multicenter Study of Six Experienced Prostate Radiologists. Radiology. 2016;280:793-804.
[96] Gaziev G, Wadhwa K, Barrett T, et al. Defining the learning curve in the implementation of multi-parametric MRI for image guided prostate biopsies.
[97] Brimo F, Schultz L, Epstein JI. The value of mandatory second opinion pathology review of prostate needle biopsy interpretation before radical prostatectomy. J Urol. 2010;184:126-30.
[98] Kasivisvanathan V, Ambrosi A, Giganti F, et al. A Dedicated Prostate MRI Teaching Course Improves the Ability of the Urologist to Interpret Clinically Significant Prostate Cancer on Multiparametric MRI. European Urology. 2019;75:203-4.
[99] Kasivisvanathan V, Rannikko AS, Borghi M, et al. MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. N Engl J Med. 2018.
[100] Siddiqui MM, Rais-Bahrami S, Turkbey B, et al. Comparison of MR/ultrasound fusion-guided biopsy with ultrasound-guided biopsy for the diagnosis of prostate cancer. Jama. 2015;313:390-7.
[101] Rhudd A, McDonald J, Emberton M, Kasivisvanathan V. The role of the multiparametric MRI in the diagnosis of prostate cancer in biopsy-naive men. Curr Opin Urol. 2017;27:488-94.
[102] Hu Y, Kasivisvanathan V, Simmons LAM, et al. Development and Phantom Validation of a 3-D-Ultrasound-Guided System for Targeting MRI-Visible Lesions During Transrectal Prostate Biopsy. IEEE transactions on bio-medical engineering. 2017;64:946-58.
[103] Moore CM, Giganti F, Albertsen P, et al. Reporting Magnetic Resonance Imaging in Men on Active Surveillance for Prostate Cancer: The PRECISE Recommendations-A Report of a European School of Oncology Task Force. Eur Urol. 2017;71:648-55.
[104] Panebianco V, Salciccia S, Cattarino S, et al. Use of multiparametric MR with neurovascular bundle evaluation to optimize the oncological and functional management of patients considered for nerve-sparing radical prostatectomy. J Sex Med. 2012;9:2157-66.

[105] Park BH, Jeon HG, Jeong BC, et al. Influence of magnetic resonance imaging in the decision to preserve or resect neurovascular bundles at robotic assisted laparoscopic radical prostatectomy. J Urol. 2014;192:82-8.
[106] Tan N, Margolis DJ, McClure TD, et al. Radical prostatectomy: value of prostate MRI in surgical planning. Abdom Imaging. 2012;37:664-74.
[107] Kasivisvanathan V, Emberton M, Ahmed HU. Focal therapy for prostate cancer: rationale and treatment opportunities. Clin Oncol (R Coll Radiol). 2013;25:461-73.
[108] Guillaumier S, Peters M, Arya M, et al. A Multicentre Study of 5-year Outcomes Following Focal Therapy in Treating Clinically Significant Nonmetastatic Prostate Cancer. European Urology. 2018;74:422-9.
[109] Obuchowski NA. Multireader, multimodality receiver operating characteristic curve studies: hypothesis testing and sample size estimation using an analysis of variance approach with dependent observations. Acad Radiol. 1995;2 Suppl 1:S22-9; discussion S57-64, S70-1 pas.
[110] Liu W, Pantoja-Galicia N, Zhang B, et al. Generalized linear mixed models for multi-reader multi-case studies of diagnostic tests. Stat Methods Med Res. 2017;26:1373-88.
[111] Davison AC HD. Bootstrap Methods and their Application. Cambridge: Cambridge University Press, 1997.
[112] Fleiss JL, Cohen J, Everitt BS. Large sample standard errors of kappa and weighted kappa. Psychological bulletin. 1969;72:323-7.
[113] Good PA. Permutation, parametric, and bootstrap tests of hypotheses: Springer, 2005.
[114] Akin O, Riedl CC, Ishill NM, Moskowitz CS, Zhang J, Hricak H. Interactive dedicated training curriculum improves accuracy in the interpretation of MR imaging of prostate cancer. Eur Radiol. 2010;20:995-1002.
[115] Ronza FM, Setola SV, Granata V, et al. Young radiologist learning curve in MRI/MRS prostate cancer evaluation: preliminary result. European Society of Radiology2011.
[116] Rosenkrantz AB, Ayoola A, Hoffman D, et al. The Learning Curve in Prostate MRI Interpretation: Self-Directed Learning Versus Continual Reader Feedback. AJR Am J Roentgenol. 2017;208:W92-W100.

[117] Latchamsetty KC, Borden LS, Jr., Porter CR, et al. Experience improves staging accuracy of endorectal magnetic resonance imaging in prostate cancer: what is the learning curve? Can J Urol. 2007;14:3429-34.
[118] Kayhan A, Fan X, Oommen J, Oto A. Multi-parametric MR imaging of transition zone prostate cancer: Imaging features, detection and staging. World J Radiol. 2010;2:180-7.
[119] Nevoux P, Ouzzane A, Ahmed HU, et al. Quantitative tissue analyses of prostate cancer foci in an unselected cystoprostatectomy series. BJU Int. 2011.
[120] Padhani AR, Weinreb J, Rosenkrantz AB, Villeirs G, Turkbey B, Barentsz J. Prostate Imaging-Reporting and Data System Steering Committee: PI-RADS v2 Status Update and Future Directions. European Urology. 2018.
[121] Rouvière O, Puech P, Renard-Penna R, et al. Use of prostate systematic and targeted biopsy on the basis of multiparametric MRI in biopsy-naive patients (MRI-FIRST): a prospective, multicentre, paired diagnostic study. The Lancet Oncology. 2019;20:100-9.
[122] Numao N, Ito M, Uchida Y, et al. 211 Optimal number of sampling cores in MRI-targeted biopsy. European Urology Supplements. 2015;14:e211.
[123] Turkbey B, Rosenkrantz AB, Haider MA, et al. Prostate Imaging Reporting and Data System Version 2.1: 2019 Update of Prostate Imaging Reporting and Data System Version 2. European Urology. 2019.
[124] Prostate Cancer NICE Gudielines Announcement, National Institute for Health and Care Excellence. Available from: https://www.nice.org.uk/news/article/non-invasive-mri-scan-for-prostate-cancer-recommended-by-nice. Accessed on 6th February 2019.
[125] Boesen L, Nørgaard N, Løgager V, et al. Assessment of the diagnostic accuracy of biparametric magnetic resonance imaging for prostate cancer in biopsy-naive men: The biparametric mri for detection of prostate cancer (bidoc) study. JAMA Network Open. 2018;1:e180219.
[126] Kum F, Elhage O, Maliyil J, et al. Initial outcomes of local anaesthetic freehand transperineal biopsies in the outpatient setting. BJU Int. 2018.
[127] Washino S, Okochi T, Saito K, et al. Combination of prostate imaging reporting and data system (PI-RADS) score and prostate-specific antigen (PSA) density predicts biopsy outcome in prostate biopsy naive patients. BJU Int. 2017;119:225-33.

[128] Chau EM, Arya M, Petrides N, et al. Performance characteristics of multiparametric-MRI at a non-academic hospital using transperineal template mapping biopsy as a reference standard. International Journal of Surgery Open. 2018;10:66-71.
[129] Wysock JS, Rosenkrantz AB, Huang WC, et al. A Prospective, Blinded Comparison of Magnetic Resonance (MR) Imaging-Ultrasound Fusion and Visual Estimation in the Performance of MR-targeted Prostate Biopsy: The PROFUS Trial. Eur Urol. 2013.
[130] Suardi N, Moschini M, Gallina A, et al. Nerve-sparing approach during radical prostatectomy is strongly associated with the rate of postoperative urinary continence recovery. BJU Int. 2013;111:717-22.
[131] Wilt TJ, Jones KM, Barry MJ, et al. Follow-up of Prostatectomy versus Observation for Early Prostate Cancer. N Engl J Med. 2017;377:132-42.
[132] Mottet N, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. Eur Urol. 2017;71:618-29.
[133] Mottet N, van den Bergh RCN, Briers E, et al. 2019 EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer. Available from: https://uroweb.org/guidelines/. Accessed 3 April 2019. .
[134] NICE. Prostate cancer: diagnosis and management (2019 update) [GID-NG10057]. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ng10057. Accessed 3 April 2019.