National Institute for Health and Care Excellence

FINAL

Prostate cancer: diagnosis and management

[D] Evidence review for diagnosing and identifying clinically significant prostate cancer

NICE guideline NG131

Evidence reviews

May 2019

These evidence reviews were developed by the NICE Guideline Updates Team

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Contents

RQ1 Diagnosing clinically significant prostate cancer

Review question

- Which of the following, alone or in combination, constitutes the most clinically- and cost- effective pathway for diagnosing prostate cancer: Multiparametric MRI; Transrectal ultrasonography (TRUS) biopsy; Transperineal template biopsy?

Introduction

This review question aims to capture one of the key themes which prompted early upgrade of the 2014 NICE Guidance CG175: how is the clinical suspicion of prostate cancer best investigated?

Template biopsy must be the most comprehensive test for identifying prostate cancer, but universal application of this diagnostic approach would have significant cost and morbidity implications, as well as placing an impossible strain on health care services. Template biopsy was therefore used as the standard against which the diagnostic accuracy of mpMRI and/or TRUS biopsy were gauged.

Evidence from diagnostic test accuracy studies and from randomised controlled trials was used, as set out in PICO tables 1 and 2. For full protocols please see Appendix A.

Table 1: PICO table –Diagnostic test accuracy studies

Population	• People with suspected prostate cancer
Index tests	• Multiparametric MRI • Multiparametric MRI targeted biopsy • TRUS biopsy alone (systematic or standard) *TRUS biopsy also referred to as saturation or extended biopsy*
Reference standard	• Transperineal template biopsy
Outcomes	• Diagnostic yield • Diagnostic accuracy ○ Sensitivity and specificity ○ Likelihood ratios *If available from studies reporting diagnostic accuracy we will also extract information on:* • Number of Adverse events ○ Haemorrhage ○ Sepsis ○ Failure to diagnose ○ Pain ○ Sexual dysfunction ○ Urine retention ○ Hospitalisation ○ Prostatitis

	• Missed cancers • Health-related quality of life - • If reported – psychological aspects of quality of life to be reported separately

Table 2: PICO table –Randomised control studies

Population	• People with suspected prostate cancer
Intervention	• Multiparametric MRI • Multiparametric MRI targeted biopsy • TRUS biopsy alone (systematic or standard) *TRUS biopsy also referred to as saturation or extended biopsy*
Control	• Multiparametric/biparametric MRI alone • MRI influenced TRUS biopsy (MRI-targeted and MRI-guided TRUS biopsy) • TRUS biopsy alone (systematic or standard *TRUS biopsy also referred to as saturation or extended biopsy*
Outcomes	• Proportion of men with clinically significant cancer (as defined by the studies) • Proportion of men who go on to definitive local or systemic treatment • Proportion of men with clinically insignificant cancer detected • Proportion of men who avoided biopsy • Proportion or Number of Adverse events • Haemorrhage • Sepsis • Failure to diagnose • Pain • Sexual dysfunction • Urine retention • Hospitalisation • Prostatitis • Missed cancers • Health-related quality of life - for example: • European Organisation for Research and Treatment of Cancer quality of life, • EPIC instrument • If reported – psychological aspects of quality of life to be reported separately

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A, and the methods section in appendix B.

Declarations of interest were recorded according to NICE's 2014 and 2018 conflicts of interest policy

This review was conducted as part of a larger update of the NICE Prostate Cancer guideline (CG175).

Clinical evidence

Included studies – diagnostic cross sectional studies

A systematic literature search for diagnostic cross-sectional studies and systematic reviews of diagnostic cross-sectional studies with a date limit of no earlier than 2007 yielded 5,716 references. These were screened on title and abstract, with 185 full-text papers ordered as potentially relevant diagnostic cross sectional studies primary studies and systematic reviews. Diagnostic cross-sectional studies were excluded if they did not meet the criteria of enrolling patients, they did not include the index tests and the reference standard as specified in the protocol. Studies were further excluded at data extraction if it was impossible to calculate sensitivity and specificity or if the study did not meet any of the other criteria stated in the protocol.

A second set of searches was conducted at the end of the guideline development process for all updated review questions using the original search strategies to capture papers published whilst the guideline was being developed. These searches, which included articles up to August 2018, returned 917 references for this review question. These were screened on title and abstract and no additional relevant references were found

Two papers were included after full text screening. Five systematic reviews were identified, however; all were excluded because the included primary studies were already part of this review (see evidence tables for details – appendix E).

Included studies – Randomised control studies

A systematic literature search for randomised controlled trials (RCTs) and systematic reviews of RCTs with a date limit of no earlier than 2007 yielded 2,488 references. These were screened on title and abstract, with 52 full-text papers ordered as potentially relevant RCTs or systematic reviews of RCTs. Studies were excluded if they did not meet the criteria of enrolling patients with suspected cancer who were biopsy naïve, they did not include the intervention and control as specified in the protocol. Studies were later excluded at data extraction if they failed to meet any of the other criteria specified in the protocol.

A second set of searches was conducted at the end of the guideline development process for all updated review questions using the original search strategies to capture papers published whilst the guideline was being developed. These searches, which included articles up to August 2018, returned 195 references for this review question. These were screened on title and abstract and no additional relevant references were found.

Two papers were included after full text screening. Three systematic reviews were identified, however; all were excluded because their included RCTs did not meet the protocol. (See evidence tables for details – appendix E).

Summary of included studies

Overall there were 4 included studies – 2 providing evidence as diagnostic cross sectional studies and 2 providing evidence as randomised control trials.

For the full evidence tables and full GRADE profiles for included studies, please see appendix E and appendix G.

Excluded studies

Details of the studies excluded at full-text review are given in appendix H along with a reason for their exclusion.

Summary of clinical studies included in the evidence review

Table 3: Summary of studies for diagnosing prostate cancer in people suspected to have prostate cancer (cross-sectional studies)

Study (year)	N	Prior biopsy	Index test	Reference Standard	Unit of Analysis	MRI Criteria for Biopsy[1]	Significant disease definition
Ahmed (2017) UK	576	No	1. MP-MRI comprising of 1.5 T magnetic field strength. T1-weighted, T2-weighted, diffusion weighted and dynamic gadolinium contrast-enhanced imaging sequences were acquired 2. TRUS biopsy	Transperineal template prostate mapping biopsy	Patient	5 Likert scale Score ≥ 3 (1, very low level of suspicion; 2, low level of suspicion; 3, equivocal; 4, cancer probable; 5, definitely cancer).	1. UCL definition 1: Gleason ≥4+3 and/or maximum cancer core length (CCLmax) ≥6mm 2. UCL definition 2: Gleason ≥3+4 and/or CCLmax ≥4mm
Nafie (2014) UK	50	No	TRUS Biopsy – 12 TRUS guided core biopsies were taken with 6 each from the right and left peripheral zones	Systematic template prostate mapping biopsy using brachytherapy grid under general anaesthesia.	Patient	n/a	1. Any cancer

Table 4: Summary of studies for diagnosing prostate cancer in people suspected to have prostate cancer (randomised control studies)

Study (year)	N	Prior biopsy	Intervention Group	Control Group	Inclusion criteria	Disease definition
Kasivisnathan (2018) (UK)	500	No	MRI and MRI targeted biopsy	Standard TRUS biopsy *A total of 10-12 biopsy cores were obtained from the peripheral zone*	- PSA level of 20ng/ml or less - Abnormal DRE and not suggestive of extracapsular disease	**Clinically significant** Disease of Gleason score 3+4 (Gleason sum of 7) or greater **Clinically insignificant** • Gleason score 3+3
Porpiglia (2017) (Italy)	212	No	MRI and MRI targeted biopsy *Biopsies were performed via either transrectal or transperineal approach based on the location of the region of interest.*	Standard TRUS biopsy *12 biopsy cores were obtained*	-prostate-specific antigen (PSA) level ≤15ng/ml -negative digital rectal examination results	**Clinically significant** • MCCL ≥5mm or Gleason ≥ 7 disease

See appendix E for full evidence tables.

Quality assessment of clinical studies included in the evidence review

See appendix G for full GRADE tables.

Economic evidence

Standard health economics filters were applied to the clinical search strategy for this review question. In total, 802 references were returned, of which 790 could be confidently excluded on screening of titles and abstracts. The remaining 12 studies were reviewed in full text, and 11 were found not to be relevant. This left 1 unique cost–utility analysis.

Included studies

One cost–utility analysis was included.

Excluded studies

Details of studies excluded after consideration at the full-text stage are provided in appendix H.

Summary of studies included in the economic evidence review

Faria et al. (2018) developed a cost-effectiveness model for lifetime health outcomes and costs, using data captured in PROMIS, a paired-cohort diagnostic study (Ahmed et al., 2017), adopting the perspective of the UK NHS and using 2015 prices. Patients at study entry were people at risk of prostate cancer referred to secondary care for further investigation.

The study assessed the performance of 3 tests: multi-parametric magnetic resonance imaging (MP-MRI), trans-rectal ultra-sound biopsy (TRUS) and transperineal mapping biopsy (TPMB). In the economic analysis, the combination of TRUS and TPMB, whichever was most severe, was the reference standard. The model examined 383 diagnostic strategies, based on possible sequences of the 3 tests, 2 pathological definitions of clinically significant prostate cancer (CS PC) and different thresholds of Likert score at which prostate cancer is considered clinically significant using MP-MRI.

A decision tree model was structured to model the diagnostic stage. The long-term stage used a Markov structure to model the lifetime costs and health benefits of people diagnosed with clinically significant (CS), non-clinically significant (NCS) or no cancer (NC), by whether they were correctly classified or not. The Markov model consisted of 2 health states for no cancer: alive or dead, and 3 health states for men with cancer: localised, metastatic and dead.

Diagnostic accuracy data were obtained from PROMIS, if possible, and also identified from other published literature, as diagnostic accuracy data varied according to the diagnostic test position in the sequence and whether it was combined with other test(s). Risk of mortality and progression included in the long-term model were derived from a clinical trial in the US: Prostate Cancer Intervention Versus Observation Trial (PIVOT). Patients misclassified as no cancer were assigned probability of progression or death observed in the watchful waiting arm, whereas data for those correctly diagnosed with cancer were taken from the radical treatment arm. Cases with

underlying prostate cancer, misclassified as having no cancer, were not considered for re-testing; thus, they would stay on active surveillance. The cost effectiveness of a strategy was defined based on number of CS cancer detected for a given pound spent in the diagnostic stage, while the long-term cost effectiveness was defined based on the maximum health outcome achieved given the cost.

Health-related utilities were derived from EQ-5D questionnaires collected in PROMIS, where TPM directly affected the health-related quality of life, while TRUS and MP-MRI were assumed to have no effect. Disutility, assigned due to aging and progression for health states in the long-run, were identified in published literature.

When the total expected lifetime cost and effectiveness results of the all 383 strategies were compared with each other, the authors found that only 14 strategies were expected to be cost effective at different values of cost-effectiveness thresholds. The strategy that was found to be optimal (when QALYs are valued at less than £30,000 each) was called "M7 222":

- all people receive MP-MRI
- people with lesion volume <0.2 cc on MP-MRI and/or assessed by the radiologist as highly likely benign (score 1 on a 5-point Likert scale reflecting probability of malignancy) are judged not to have clinically significant prostate cancer
- people with lesion volume ≥0.2 cc and/or Gleason score ≥3+4, assessed by the radiologist as ≥2 on the Likert scale undergo MRI-targeted TRUS biopsy
    - people with any Gleason ≥3+4 and/or cancer core length ≥4 mm are diagnosed with clinically significant prostate cancer
    - people not meeting these criteria receive a 2nd MRI-targeted TRUS biopsy
        - people with any Gleason ≥3+4 and/or cancer core length ≥4 mm are diagnosed with clinically significant prostate cancer
        - people not meeting these criteria are judged not to have clinically significant prostate cancer
- template biopsies are not used in this strategy

This strategy (which was the 2nd most effective of those simulated) had an ICER of £7,076/QALY compared with the next best strategy. The most effective strategy (P4 2--) was for all people to receive TRUS biopsy, after which anyone with negative findings undergoes template biopsy. However, this strategy was associated with an ICER of £30,084/QALY compared with M7 222.

The results are sensitive to the sensitivity of the 1st and 2nd MRI-targeted TRUS and the costs of the test. For example, a reduction in the sensitivity assigned to MRI-targeted TRUS resulted in the cost-effectiveness results favouring strategies beginning with TRUS.

Economic model

This question was not prioritised for economic modelling.

Evidence statements

The evidence statements in these sections are written with reference to the size of the likelihood ratios in the GRADE tables in appendix G, using the interpretation detailed in the methods section on diagnostic test accuracy (Table 6).

Clinical evidence statements from cross sectional studies

Evidence on TRUS biopsy shows that

- A positive TRUS biopsy leads to a **very large increase** in the probability that a person suspected of prostate cancer has clinically significant disease (high quality evidence form 2 prospective studies comprising 626 participants; 95% confidence intervals range from large to very large increase).
- A negative TRUS biopsy **does not meaningfully alter the probability** that a person suspected of prostate cancer has clinically significant disease (Moderate-quality evidence from 2 prospective studies comprising 626 participants; 95% confidence intervals range from slight to moderate decrease).

Evidence on multiparametric MRI shows that

- *Results that indicate a person suspected of prostate cancer has an increased probability of clinically significant disease (based on positive likelihood ratios)*:
  - A score of ≥2 **does not alter the probability** that a person suspected of prostate cancer has clinically significant disease (high-quality evidence from 1 prospective study comprising 576 participants; 95% confidence intervals range from slight decrease to slight increase).
  - A score of ≥3 **does not alter the probability** that a person suspected of prostate cancer has clinically significant disease (high-quality evidence from 1 prospective study comprising 576 participants; 95% confidence intervals range within slight increase).
  - A score of ≥4 leads to a **moderate increase** in the probability that a person suspected of prostate cancer has clinically significant disease (high-quality evidence from 1 prospective study comprising 576 participants; 95% confidence intervals range from slight increase to large increase).
  - A score of ≥5 leads to a **large increase** in the probability that a person suspected of prostate cancer has clinically significant disease (low-quality evidence from 1 prospective study comprising 576 participants; 95% confidence intervals range from slight increase to very large increase).
- *Results that indicate a person suspected of prostate cancer has a decreased probability of clinically significant disease (based on negative likelihood ratios):*
  - A score of <2 leads to a **moderate decrease** in the probability that a person suspected of prostate cancer has clinically significant disease high-quality evidence from 1 prospective study comprising 576 participants; 95% confidence intervals range from slight to large decrease).
  - A score of <3 leads to a **large decrease** in the probability that a person suspected of prostate cancer has clinically significant disease (high-quality evidence from 1 prospective study comprising 576 participants; 95% confidence intervals range from moderate to large decrease).

- A score of <4 leads to a **moderate decrease** in the probability that a person suspected of prostate cancer has clinically significant disease (high-quality evidence from 1 prospective study comprising 576 participants; 95% confidence intervals range within moderate decrease).
- A score of <5 does **not alter the probability** that a person suspected of prostate cancer has clinically significant disease (high-quality evidence from 1 prospective study comprising 576 participants; 95% confidence intervals range within slight decrease).

Clinical evidence statements from randomised control studies

MRI influenced TRUS biopsy versus systematic TRUS biopsy

Very low-quality evidence from 2 RCTs including 712 people who are biopsy naïve and suspected of having prostate cancer shows that MRI-influenced-prostate biopsy finds more people with clinically significant cancer than systematic prostate biopsy.

High-quality evidence from 2 RCTs including 712 people who are biopsy naïve and suspected of having prostate cancer shows that MRI-influenced prostate biopsy finds less people with clinically insignificant cancer than systematic prostate biopsy.

High-quality evidence from 2 RCT including 456 people who are biopsy naïve and suspected of having prostate cancer shows that using a strategy which includes MRI as first line treatment may lead to a quarter of people avoiding repeat biopsy.

Low-quality evidence from 1 RCT including 500 people who are biopsy naïve and suspected of having prostate cancer could not differentiate investigator-reported adverse events (sepsis, haematuria and prostatitis) between people who had MRI-influenced-prostate biopsy and those who had systematic prostate biopsy.

High-quality evidence from 1 RCT including 500 people who are biopsy naïve and suspected of having prostate cancer shows there is no difference in health-related quality of life between people having MRI-influenced-prostate biopsy and those having systematic prostate biopsy at 24 hours and at 30 days post biopsy.

Moderate- to high-quality evidence from 1 RCT reporting data on 418 people who are biopsy naïve and suspected of having prostate cancer found fewer people who had MRI-influenced-biopsy reported blood in the urine, blood in semen and pain at site of procedure than those who had systematic TRUS-guided biopsy. However, the evidence could not differentiate the number of people experiencing other adverse events such as erectile dysfunction, urinary tract infection, prostatitis and urinary incontinence between the 2 groups.

Economic evidence statement

One directly applicable cost–utility analysis with minor limitations found that the optimal diagnostic strategy is for all people to receive MP-MRI followed by up to 2 MRI-targeted TRUS biopsies for those with positive findings. This strategy was associated with an ICER of £7,076/QALY compared with the next-best option.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee was interested in negative and positive predictive values as this is what they were familiar with. The development team explained the limitations associated with reporting evidence in terms of negative and positive predictive values as they depend on the prevalence of disease within the study population. As a result, likelihood ratios were deemed to be the superior option and thus the outcome of most importance when considering diagnostic test studies

When considering evidence from randomised control studies, the committee was interested in the proportion of people with clinically significant cancer following MRI influenced biopsy. This was because there was no evidence for MRI incluenced biopsy from the diagnostic test accuracy studies.

The quality of the evidence

The 2 included studies for diagnostic test accuracy were of moderate quality (Nafie et al. 2014) owing to unclear patient selection or low risk of bias (Ahmed et al. 2017). The committee acknowledged that this was an area with new emerging evidence, therefore they were not surprised by the limited amount of studies. Both of the studies were prospective cross-sectional studies from the UK.

The PROMIS study (Ahmed et al. 2017), is a well conducted large UK diagnostic accuracy study with a large population of 576 participants. This study contributed evidence for both TRUS biopsy and multiparametric-MRI. The study by Nafie et al. (2014) was also well conducted but with a smaller sample size investigating the diagnostic accuracy of TRUS biopsy. As a result only 1 study contributed to the evidence on multiparametric-MRI (Ahmed et al. (2017) and 2 studies on TRUS biopsy (Ahmed et al. (2017) and Nafie et al. (2014)).

There were no diagnostic test accuracy studies included addressing MRI influenced prostate biopsy. As a result the committee was also presented with evidence from diagnostic randomised control trial studies.

Initially 5 studies were included, however the committee agreed that 3 of the studies Baco et al. (2016), Park et al.(2011) and Tontilla et al. (2016), were out of date as their study periods were almost 10 years ago. The committee noted that MRI technology has changed significantly since then and they were only interested in the most recent studies that reflect current practice. Though the Baco et al. and Tontilla et al. studies were published in 2016, the studies were started in 2011, the committee explained that, the technology during that period has changed considerably. This resulted in the review of 2 papers Kasivisnathan et al. (2018) (also referred to as the PRECISION study) and Porpiglia et al. (2017).

These 2 studies were graded as having low risk of bias. The PRECISION study (Kasivisvanathan et al. (2018) is a UK study and Porpiglia et al. (2017) is an Italian study. Both studies provided evidence for MRI influenced prostate biopsy. The committee opted for the term "prostate biopsy" because some of the participants from the Kasivisnathan et al. (2018)

study had biopsy taken via the transperineal route and not the transrectal route, the committee noted that “prostate biopsy” encompasses both terms. There currently is limited evidence on the efficacy of transperineal (not mapping biopsy), for the purposes of this review performance of transperineal route was assumed to be similar to that of transrectal route biopsy.

Benefits and harms

Clinical effectiveness

Based on the evidence, the committee recommended multiparametric MRI as the first-line investigation for people with suspected clinically localised prostate cancer. Evidence from the PRECISION study (Kasivisvanathan et al. (2018) and Porpiglia et al. (2017) showed that more people with clinically significant cancers were likely to be identified if they had MRI influenced biopsy than if they received prostate biopsy alone.

The PRECISION study (Kasivisvanathan et al. (2018) carried out MRI-influenced prostate biopsy in those people whose multiparametric-MRI Likert score was 3 or above; however, PROMIS (Ahmed et al., 2017) and the Porpiglia et al. (2017) trial provided evidence that there is a risk that clinically significant cancers may be missed if a cutoff of Likert 3 is used to classify MRI findings. As a result, the committee made 'consider' recommendations to omit prostate biopsy in people with a multiparametric-MRI Likert score of 1 or 2. The committee stressed that, for those with a MRI Likert score of 1 or 2, there should be a discussion of risks and benefits before reaching a shared decision. As a result, a preference decision point was developed to help clinicians explain advantages and disadvantages of undergoing TRUS biopsy in people with low-risk MRI findings. To inform this advice, data on the accuracy of MRI and the accuracy of TRUS biopsy in people with low-risk MRI findings were obtained from the PROMIS trial (previously unpublished data on the sensitivity of TRUS biopsy stratified by MRI findings were provided by the PROMIS investigators; for details, see table HE05 in Health economics report). Data on the adverse events associated with TRUS biopsy were derived from the ProtecT RCT (Rosario et al., 2012). To use these data, it was assumed that

- both tests (multiparametric MRI and TRUS biopsy) will perform similarly in practice as they did in the PROMIS trial, and
- the population recruited for the study is representative of people who are suspected of prostate cancer in practice; in particular, there is a similar prevalence of clinically significant prostate cancer among PROMIS participants as there is in the population that would be considered for testing in practice. This assumption is important, as the information the committee suggest should be used to guide decision-making includes data derived from predictive values. These will only be valid for populations with the same underlying prevalence of disease as the cohort in the study. However, the committee agreed that, because it was undertaken in the UK and had broad eligibility criteria, PROMIS is a good source of evidence on the true prevalence of clinically significant prostate cancer (when measured using a reliable standard – TPM biopsy) as well as on the performance of MRI and TRUS biopsy. Therefore, the committee was content that predictive values from PROMIS should have a good degree of applicability in NHS practice.

Evidence from the PROMIS study showed that a multiparametric- MRI Likert score of less than 3 leads to a large decrease in the probability that a person suspected of prostate cancer has clinically significant disease, as a result the committee recommended that multiparametric MRI -

influenced prostate biopsy should be offered in people whose multiparametric-MRI Likert score is 3 or more.

Considering the accuracy of multiparametric MRI, the committee made a ‘do not offer’ recommendation on the use of mapping transperineal template biopsy as an initial assessment. The committee explained that this type of biopsy is very invasive requiring patients to be under general anaesthetics, and requiring at least 24 samples to be taken. It also explained that transperineal template biopsy is resource intensive and the NHS is not equipped to perform large numbers of these. The committee was also concerned by the potential for over diagnosis and high numbers of clinically non-significant disease are identified.

The committee did not change the existing recommendation that imaging should not be offered to people who are not suitable for for radical treatment because no new evidence was found that affects current recommended practice.

Cost effectiveness

The committee reviewed the included economic evidence. It agreed that the included cost-utility analysis provided directly applicable evidence, as it was based on a UK RCT (PROMIS). The committee noted some limitations of the analyses, particularly that the MRI-influenced biopsy technique was not explicitly explained, which affected the sensitivity parameter assigned to this test. In addition, there was a high degree of uncertainty around the cost-effectiveness of the long-term treatment, in particular for those with low-risk prostate cancer. This influenced the selection of the MP-MRI cut-off point at which patient were directed to biopsy. However, the committee were shown the two-way sensitivity analysis that assessed the impact of changes in two parameters: the relative sensitivity of the MRI-influenced biopsy and its cost. They were convinced that the optimal strategy suggested by PROMIS economic study was maintained within plausible ranges.

The committee agreed that limitations of the economic evidence provided by PROMIS would not alter its conclusion. Thus it concluded that the data provided by PROMIS are sufficient to underpin its recommendation about considering the diagnostic strategy suggested by PROMIS and found to be the most optimal in diagnosing prostate cancer.

Other factors the committee took into account

The committee discussed the term ‘clinically significant cancer’ and agreed that there was no universally agreed definition of the term. The definition used in this review generally meant cancer of Gleason 7 or greater as reported by the included studies.

The committee also discussed whether or not there should be a specific mention of which contrast enhancement agent to use with multiparametric MRI. The committee decided to leave this decision with the imaging centres and specified that the MRI protocol should be multiparametric – which includes at least 1.5 Tesla, diffusion weighted, contrast- enhanced imaging and b value of at least 800.

Appendices

Appendix A – Review protocols

RQ1 - Review protocol for prostate cancer diagnosis in men with suspected prostate (diagnostic cross-sectional studies)

ID	Field (based on PRISMA-P)	Content
I	Review question	Which of the following, alone or in combination, constitutes the most clinical and cost- effective pathway for diagnosing prostate cancer: • Multiparametric or biparametric MRI alone • MRI influenced TRUS biopsy (MRI-targeted and MRI-guided TRUS biopsy) • TRUS biopsy alone (systematic) • Transperineal template biopsy *TRUS biopsy also referred to as saturation or extended biopsy*
II	Type of review question	Diagnostic accuracy
III	Objective of the review	To assess whether undertaking MRI prior to biopsy increases diagnostic yield and to determine which of the following, alone or in combination, constitutes the most clinical and cost-effective pathway for diagnosing prostate cancer: • Multiparametric or biparametric MRI alone • MRI influenced TRUS biopsy (MRI-targeted and MRI-guided TRUS biopsy) • TRUS biopsy alone (systematic) Transperineal template biopsy *This question was identified as requiring updating during the 2016 exceptional surveillance review. Recommendations may be made on where MRI should feature in the diagnostic pathway.*
IV	Eligibility criteria – population	People with suspected prostate cancer

V	Index Tests	• Multiparametric or biparametric MRI alone • MRI influenced TRUS biopsy (MRI-targeted and MRI-guided TRUS biopsy,) • TRUS biopsy alone (systematic or standard) • *TRUS biopsy also referred to as saturation or extended biopsy*
VI	Reference (gold) standard	• Transperineal template biopsy (*also referred to as mapping)*
VII	Outcomes	Diagnostic yield Diagnostic accuracy • Sensitivity and specificity • Likelihood ratios *If available from studies reporting diagnostic accuracy we will also extract information on*: • Number of Adverse events ○ Haemorrhage ○ Sepsis ○ Failure to diagnose ○ Pain ○ Sexual dysfunction ○ Urine retention ○ Hospitalisation ○ Prostatitis ○ Missed cancers • Health-related quality of life - for example: ○ European Organisation for Research and Treatment of Cancer quality of life, ○ EPIC instrument *If reported – <u>psychological aspects</u> of quality of life to be reported separately*
VIII	Eligibility criteria – study design	• Diagnostic cross-sectional studies • Systematic reviews of diagnostic cross-sectional studies
IX	Other exclusion criteria	• Non English- language papers will be excluded • Case-control studies • Retrospective studies • Screening studies

		• Studies in people with an established diagnosis of prostate cancer at the time of diagnostic assessments
X	Proposed sensitivity/sub-group analysis, or meta-regression	None identified
XI	Selection process – duplicate screening/selection/analysis	10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. If meaningful disagreements are found between the different reviewers, a further 10% of the abstracts will be reviewed by two reviewers, with this process continued until agreement is achieved between the two reviewers. From this point, the remaining abstracts will be screened by a single reviewer.
XII	Data management (software)	See Appendix B – section 1.3
XIII	Information sources – databases and dates	See appendix C of the relevant chapter
XIV	Identify if an update	Update of 2014 prostate cancer guideline question: Does multiparametric/functional MRI before TRUS biopsy increase diagnostic yield of initial biopsy in men with suspected prostate cancer? Since the question is substantially different, a new review protocol has been developed. **List of recommendations that may be affected** 1.2.6 Consider multiparametric MRI (using T2- and diffusion-weighted imaging) for men with a negative transrectal ultrasound 10–12 core biopsy to determine whether another biopsy is needed. **[new 2014]** 1.2.7 Do not offer another biopsy if the multiparametric MRI (using T2- and diffusion-weighted imaging) is negative, unless any of the risk factors listed in recommendation 1.2.5 are present. **[new 2014]**

		1.2.8 Determine the provisional treatment intent (radical or non-radical) before decisions on imaging are made. **[2008]** 1.2.9 Do not routinely offer imaging to men who are not candidates for radical treatment. **[2008]** 1.2.11 Consider multiparametric MRI, or CT if MRI is contraindicated, for men with histologically proven prostate cancer if knowledge of the T or N stage could affect management. **[new 2014]**
XV	Author contacts	Guideline updates team, National Institute for Health and Care Excellence (contact adam.okeefe@nice.org.uk)
XVI	Highlight if amendment to previous protocol	This is not an amendment to a previous protocol.
XVII	Search strategy – for one database	For details please see appendix C of relevant chapter. Searches run from 2007 on advice from the guideline committee.
XVIII	Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix E (clinical evidence tables) or H (economic evidence tables). 10% of data will be extracted by 2 reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. If meaningful disagreements are found between the different reviewers, a further 10% of the data will be extracted by 2 reviewers, with this process continued until agreement is achieved between the 2 reviewers.
XIX	Data items – define all variables to be collected	For details please see evidence tables in appendix E (clinical evidence tables) or H (economic evidence tables). Further detail on NICE evidence tables is available in section 6.4 of Developing NICE guidelines: the manual.
XX	Methods for assessing bias at outcome/study level	See Appendix B below – see section 1.6
XXI	Criteria for quantitative synthesis (where suitable)	See Appendix B below

XXII	Methods for analysis – combining studies and exploring (in)consistency	See Appendix B below – see section 1.6.2
XXIII	Meta-bias assessment – publication bias, selective reporting bias	See Appendix B below – see section 1.6.3 and 1.6.5
XXIV	Assessment of confidence in cumulative evidence	See Appendix B below - see section 1.6.3
XXV	Rationale/context – Current management	For details please see the introduction to the evidence review in the main file.
XXVI	Describe contributions of authors and guarantor	A multidisciplinary committee will develop the guideline update. The committee was convened by the NICE Guideline Updates Team and chaired by Waqaar Shah in line with section 3 of Developing NICE guidelines: the manual. Staff from NICE will undertake systematic literature searches, appraise the evidence, conduct meta-analyses and cost-effectiveness analyses where appropriate, and draft the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.
XXVII	Sources of funding/support	The NICE Guideline Updates Team is an internal team within NICE.
XXVIII	Name of sponsor	The NICE Guideline Updates Team is an internal team within NICE.
XXIX	Roles of sponsor	The NICE Guideline Updates Team is an internal team within NICE.

XXX	PROSPERO registration number	N/A

RQ1a - Review protocol for prostate cancer diagnosis in men with suspected prostate (randomised control studies)

ID	Field (based on PRISMA-P)	Content
I	Review question	Which of the following, alone or in combination, constitutes the most clinical and cost- effective pathway for diagnosing prostate cancer: • Multiparametric or biparametric MRI alone • MRI influenced TRUS biopsy (MRI-targeted and MRI-guided TRUS biopsy) • TRUS biopsy alone (systematic) • Transperineal template biopsy *TRUS biopsy also referred to as saturation or extended biopsy*
II	Type of review question	Intervention
III	Objective of the review	To determine which of the following, alone or in combination, constitutes the most clinical and cost- effective pathway for diagnosing prostate cancer: • Multiparametric or biparametric MRI alone • MRI influenced TRUS biopsy (MRI-targeted and MRI-guided TRUS biopsy) • TRUS biopsy alone (systematic) Transperineal template biopsy *This question was identified as requiring updating during the 2016 exceptional surveillance review. Recommendations may be made on where MRI should feature in the diagnostic pathway.*
IV	Eligibility criteria – population	People with suspected prostate cancer

V	Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	• Multiparametric/biparamteric MRI alone • MRI influenced TRUS biopsy (MRI-targeted and MRI-guided TRUS biopsy,) • TRUS biopsy alone (systematic or standard) *TRUS biopsy also referred to as saturation or extended biopsy*
VI	Eligibility criteria – comparator(s)/control or reference (gold) standard	• Multiparametric/biparamteric MRI alone • MRI influenced TRUS biopsy (MRI-targeted and MRI-guided TRUS biopsy,) • TRUS biopsy alone (systematic or standard *TRUS biopsy also referred to as saturation or extended biopsy*
VII	Outcomes	• Proportion of men with clinically significant cancer (as defined by the studies) • Proportion of men who go on to definitive local or systemic treatment • Proportion of men with clinically insignificant cancer detected • Proportion of men who avoided biopsy • Proportion or Number of Adverse events ○ Haemorrhage ○ Sepsis ○ Failure to diagnose ○ Pain ○ Sexual dysfunction ○ Urine retention ○ Hospitalisation ○ Prostatitis ○ Missed cancers • Health-related quality of life - for example: ○ European Organisation for Research and Treatment of Cancer quality of life, ○ EPIC instrument *If reported – <u>psychological aspects</u> of quality of life to be reported separately*
VIII	Eligibility criteria – study design	• Randomised control trials • Systematic reviews of randomised control trials

IX	Other exclusion criteria	• Non English- language papers will be excluded • Case-control studies • Retrospective studies • Screening studies • Studies in people with an established diagnosis of prostate cancer at the time of diagnostic assessments
X	Proposed sensitivity/sub-group analysis, or meta-regression	• Different definitions of significant cancers • Follow –up times
XI	Selection process – duplicate screening/selection/analysis	10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. If meaningful disagreements are found between the different reviewers, a further 10% of the abstracts will be reviewed by two reviewers, with this process continued until agreement is achieved between the two reviewers. From this point, the remaining abstracts will be screened by a single reviewer.
XII	Data management (software)	See Appendix B – section 1.3
XIII	Information sources – databases and dates	See appendix C of the relevant chapter
XIV	Identify if an update	Update of 2014 prostate cancer guideline question: Does multiparametric/functional MRI before TRUS biopsy increase diagnostic yield of initial biopsy in men with suspected prostate cancer? Since the question is substantially different, a new review protocol has been developed. **List of recommendations that may be affected** 1.2.6 Consider multiparametric MRI (using T2- and diffusion-weighted imaging) for men with a negative transrectal ultrasound 10–12 core biopsy to determine whether another biopsy is needed. **[new 2014]**

		1.2.7 Do not offer another biopsy if the multiparametric MRI (using T2- and diffusion-weighted imaging) is negative, unless any of the risk factors listed in recommendation 1.2.5 are present. **[new 2014]** 1.2.8 Determine the provisional treatment intent (radical or non-radical) before decisions on imaging are made. **[2008]** 1.2.9 Do not routinely offer imaging to men who are not candidates for radical treatment. **[2008]** 1.2.11 Consider multiparametric MRI, or CT if MRI is contraindicated, for men with histologically proven prostate cancer if knowledge of the T or N stage could affect management. **[new 2014]**
XV	Author contacts	Guideline updates team, National Institute for Health and Care Excellence (contact adam.okeefe@nice.org.uk)
XVI	Highlight if amendment to previous protocol	This is not an amendment to a previous protocol.
XVII	Search strategy – for one database	For details please see appendix C of relevant chapter. Searches run from 2007 on advice from the guideline committee.
XVIII	Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix E (clinical evidence tables) or H (economic evidence tables). 10% of data will be extracted by 2 reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. If meaningful disagreements are found between the different reviewers, a further 10% of the data will be extracted by 2 reviewers, with this process continued until agreement is achieved between the 2 reviewers.
XIX	Data items – define all variables to be collected	For details please see evidence tables in appendix E (clinical evidence tables) or H (economic evidence tables). Further detail on NICE evidence tables is available in section 6.4 of Developing NICE guidelines: the manual.
XX	Methods for assessing bias at outcome/study level	See Appendix B below – see section 1.6

XXI	Criteria for quantitative synthesis (where suitable)	See Appendix B below
XXII	Methods for analysis – combining studies and exploring (in)consistency	See Appendix B below – see section 1.6.2
XXIII	Meta-bias assessment – publication bias, selective reporting bias	See Appendix B below – see section 1.6.3 and 1.6.5
XXIV	Assessment of confidence in cumulative evidence	See Appendix B below - see section 1.6.3
XXV	Rationale/context – Current management	For details please see the introduction to the evidence review in the main file.
XXVI	Describe contributions of authors and guarantor	A multidisciplinary committee will develop the guideline update. The committee was convened by the NICE Guideline Updates Team and chaired by Waqaar Shah in line with section 3 of Developing NICE guidelines: the manual. Staff from NICE will undertake systematic literature searches, appraise the evidence, conduct meta-analyses and cost-effectiveness analyses where appropriate, and draft the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.
XXVII	Sources of funding/support	The NICE Guideline Updates Team is an internal team within NICE.
XXVIII	Name of sponsor	The NICE Guideline Updates Team is an internal team within NICE.

XXIX	Roles of sponsor	The NICE Guideline Updates Team is an internal team within NICE.
XXX	PROSPERO registration number	N/A

Appendix B – Methods

Incorporating published systematic reviews

For all review questions where a literature search was undertaken looking for a particular study design, systematic reviews containing studies of that design were also included. All included studies from those systematic reviews were screened to identify any additional relevant primary studies not found as part of the initial search.

Evidence of effectiveness of interventions

Quality assessment

Individual RCTs and quasi-randomised controlled trials were quality assessed using the Cochrane Risk of Bias Tool. Each individual study was classified into one of the following three groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.
- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.
- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, intervention, comparator and/or outcomes in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, intervention, comparator and/or outcomes.
- Partially indirect – Important deviations from the protocol in one of the population, intervention, comparator and/or outcomes.
- Indirect – Important deviations from the protocol in at least two of the following areas: population, intervention, comparator and/or outcomes.

Methods for combining intervention evidence

Meta-analyses of interventional data were conducted with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011).

Where different studies presented continuous data measuring the same outcome but using different numerical scales (e.g. a 0-10 and a 0-100 visual analogue scale), these outcomes were all converted to the same scale before meta-analysis was conducted on the mean differences. Where outcomes measured the same underlying construct but used different instruments/metrics, data were analysed using standardised mean differences (Hedges' g).

A pooled relative risk was calculated for dichotomous outcomes (using the Mantel–Haenszel method). Both relative and absolute risks were presented, with absolute risks calculated by applying the relative risk to the pooled risk in the comparator arm of the meta-analysis.

Fixed- and random-effects models (der Simonian and Laird) were fitted for all syntheses, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models were the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model were clearly not met, even after appropriate pre-specified subgroup analyses were conducted, random-effects results are presented. Fixed-effects models were deemed to be inappropriate if one or both of the following conditions was met:

- Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. This decision was made and recorded before any data analysis was undertaken.
- The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$.

In any meta-analyses where some (but not all) of the data came from studies at high risk of bias, a sensitivity analysis was conducted, excluding those studies from the analysis. Results from both the full and restricted meta-analyses are reported. Similarly, in any meta-analyses where some (but not all) of the data came from indirect studies, a sensitivity analysis was conducted, excluding those studies from the analysis.

Meta-analyses were performed in Cochrane Review Manager v5.3.

Minimal clinically important differences (MIDs)

The Core Outcome Measures in Effectiveness Trials (COMET) database was searched to identify published minimal clinically important difference thresholds relevant to this guideline. Identified MIDs were assessed to ensure they had been developed and validated in a methodologically rigorous way, and were applicable to the populations, interventions and outcomes specified in this guideline. In addition, the Guideline Committee were asked to prospectively specify any outcomes where they felt a consensus MID could be defined from their experience. In particular, any questions looking to evaluate non-inferiority (that one treatment is not meaningfully worse than another) required an MID to be defined to act as a non-inferiority margin.

For standardised mean differences where no other MID was available, an MID of 0.2 was used, corresponding to the threshold for a small effect size initially suggested by Cohen et al. (1988). For relative risks where no other MID was available, a default MID interval for dichotomous outcomes of 0.8 to 1.25 was used.

When decisions were made in situations where MIDs were not available, the ‘Evidence to Recommendations’ section of that review should make explicit the committee’s view of the expected clinical importance and relevance of the findings. In particular, this includes consideration of whether the whole effect of a treatment (which may be felt across multiple independent outcome domains) would be likely to be clinically meaningful, rather than simply whether each individual sub outcome might be meaningful in isolation.

GRADE for pairwise meta-analyses of interventional evidence

GRADE was used to assess the quality of evidence for the selected outcomes as specified in 'Developing NICE guidelines: the manual (2014)'. Data from RCTs was initially rated as high quality and the quality of the evidence for each outcome was downgraded or not from this initial point. If non-RCT evidence was included for intervention-type systematic reviews then these were initially rated as either moderate quality (quasi-randomised studies) or low quality (cohort studies) and the quality of the evidence for each outcome was further downgraded or not from this point, based on the criteria given in Table 5

Table 5: Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias.
Indirectness	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between direct and indirect studies.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded. Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level. Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies with the smallest and largest effect sizes.
Imprecision	If an MID other than the line of no effect was defined for the outcome, the outcome was downgraded once if the 95% confidence interval for the effect size crossed one line of the MID, and twice if it crosses both lines of the MID.

GRADE criteria	Reasons for downgrading quality
	If the line of no effect was defined as an MID for the outcome, it was downgraded once if the 95% confidence interval for the effect size crossed the line of no effect (i.e. the outcome was not statistically significant), and twice if the sample size of the study was sufficiently small that it is not plausible any realistic effect size could have been detected. Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.

The quality of evidence for each outcome was upgraded if any of the following three conditions were met:

- Data from non-randomised studies showing an effect size sufficiently large that it cannot be explained by confounding alone.
- Data showing a dose-response gradient.
- Data where all plausible residual confounding is likely to increase our confidence in the effect estimate.

Publication bias

Publication bias was assessed in two ways. First, if evidence of conducted but unpublished studies was identified during the review (e.g. conference abstracts, trial protocols or trial records without accompanying published data), available information on these unpublished studies was reported as part of the review. Secondly, where 10 or more studies were included as part of a single meta-analysis, a funnel plot was produced to graphically assess the potential for publication bias.

Evidence statements

Evidence statements for pairwise intervention data are classified in to one of four categories:

- Situations where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), and the magnitude of that effect is most likely to meet or exceed the MID (i.e. the point estimate is not in the zone of equivalence). In such cases, we state that the evidence showed that there is an effect.
- Situations where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), but the magnitude of that effect is most likely to be less than the MID (i.e. the point estimate is in the zone of equivalence). In such cases, we state that the evidence could not demonstrate a meaningful difference.
- Situations where the data are consistent, at a 95% confidence level, with an effect in either direction (i.e. one that is not 'statistically significant') but the confidence limits are smaller than the MIDs in both directions. In such cases, we state that the evidence demonstrates that there is no difference.
- In all other cases, we state that the evidence could not differentiate between the comparators.

For outcomes without a defined MID or where the MID is set as the line of no effect (for example, in the case of mortality), evidence statements are divided into 2 groups as follows:

- We state that the evidence showed that there is an effect if the 95% CI does not cross the line of no effect.
- We state the evidence could not differentiate between comparators if the 95% CI crosses the line of no effect.

The number of trials and participants per outcome are detailed in the evidence statements, but in cases where there are several outcomes being summarised in a single evidence statement and the numbers of participants and trials differ between outcomes, then the number of trials and participants stated are taken from the outcome with the largest number of trials. This is denoted using the terminology 'up to' in front of the numbers of trials and participants.

The evidence statements also cover the quality of the outcome based on the GRADE table entry. These can be included as single ratings of quality or go from one quality level to another if multiple outcomes with different quality ratings are summarised by a single evidence statement

Diagnostic test accuracy evidence

In this guideline, diagnostic test accuracy (DTA) data are classified as any data in which a feature – be it a symptom, a risk factor, a test result or the output of some algorithm that combines many such features – is observed in some people who have the condition of interest at the time of the test and some people who do not. Such data either explicitly provide, or can be manipulated to generate, a 2x2 classification of true positives and false negatives (in people who, according to the reference standard, truly have the condition) and false positives and true negatives (in people who, according to the reference standard, do not).

The 'raw' 2x2 data can be summarised in a variety of ways. Those that were used for decision making in this guideline are as follows:

- **Positive likelihood ratios** describe how many times more likely positive features are in people with the condition compared to people without the condition. Values greater than 1 indicate that a positive result makes the condition more likely.
  - LR^+ = (TP/[TP+FN])/(FP/[FP+TN])
- **Negative likelihood ratios** describe how many times less likely negative features are in people with the condition compared to people without the condition. Values less than 1 indicate that a negative result makes the condition less likely.
  - LR^- = (FN/[TP+FN])/(TN/[FP+TN])
- **Sensitivity** is the probability that the feature will be positive in a person with the condition.
  - sensitivity = TP/(TP+FN)
- **Specificity** is the probability that the feature will be negative in a person without the condition.
  - specificity = TN/(FP+TN)

The following schema, adapted from the suggestions of Jaeschke et al. (1994), was used to interpret the likelihood ratio findings from diagnostic test accuracy reviews.

Table 6: Interpretation of likelihood ratios

Value of likelihood ratio	Interpretation
LR ≤ 0.1	**Very large** decrease in probability of disease
0.1 < LR ≤ 0.2	**Large** decrease in probability of disease
0.2 < LR ≤ 0.5	**Moderate** decrease in probability of disease
0.5 < LR ≤ 1.0	**Slight** decrease in probability of disease
1.0 < LR < 2.0	**Slight** increase in probability of disease
2.0 ≤ LR < 5.0	**Moderate** increase in probability of disease
5.0 ≤ LR < 10.0	**Large** increase in probability of disease
LR ≥ 10.0	**Very large** increase in probability of disease

The schema above has the effect of setting a minimal important difference for positive likelihoods ratio at 2, and a corresponding minimal important difference for negative likelihood ratios at 0.5. Likelihood ratios (whether positive or negative) falling between these thresholds were judged to indicate no meaningful change in the probability of disease.

Quality assessment

Individual studies were quality assessed using the QUADAS-2 tool, which contains four domains: patient selection, index test, reference standard, and flow and timing. Each individual study was classified into one of the following two groups:

- Low risk of bias – Evidence of non-serious bias in zero or one domain.
- Moderate risk of bias – Evidence of non-serious bias in two domains only, or serious bias in one domain only.
- High risk of bias – Evidence of bias in at least three domains, or of serious bias in at least two domains.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, index features and/or reference standard in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, index feature and/or reference standard.
- Partially indirect – Important deviations from the protocol in one of the population, index feature and/or reference standard.
- Indirect – Important deviations from the protocol in at least two of the population, index feature and/or reference standard.

Methods for combining diagnostic test accuracy evidence

Meta-analysis of diagnostic test accuracy data was conducted with reference to the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (Deeks et al. 2010).

Where applicable, diagnostic syntheses were stratified by:

- Presenting symptomatology (features shared by all participants in the study, but not all people who could be considered for a diagnosis in clinical practice).

- The reference standard used for true diagnosis.

Where five or more studies were available for all included strata, a bivariate model was fitted using the mada package in R v3.4.0, which accounts for the correlations between positive and negative likelihood ratios, and between sensitivities and specificities. Where sufficient data were not available (2-4 studies), separate independent pooling was performed for positive likelihood ratios, negative likelihood ratios, sensitivity and specificity, using Microsoft Excel. This approach is conservative as it is likely to somewhat underestimate test accuracy, due to failing to account for the correlation and trade-off between sensitivity and specificity (see Deeks 2010).

Random-effects models (der Simonian and Laird) were fitted for all syntheses, as recommended in the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (Deeks et al. 2010).

In any meta-analyses where some (but not all) of the data came from studies at high risk of bias, a sensitivity analysis was conducted, excluding those studies from the analysis. Results from both the full and restricted meta-analyses are reported. Similarly, in any meta-analyses where some (but not all) of the data came from indirect studies, a sensitivity analysis was conducted, excluding those studies from the analysis.

Modified GRADE for diagnostic test accuracy evidence

GRADE has not been developed for use with diagnostic studies; therefore a modified approach was applied using the GRADE framework. GRADE assessments were only undertaken for positive and negative likelihood ratios, as the MIDs used to assess imprecision were based on these outcomes, but results for sensitivity and specificity are also presented alongside those data.

Cross-sectional and cohort studies were initially rated as high-quality evidence if well conducted, and then downgraded according to the standard GRADE criteria (risk of bias, inconsistency, imprecision and indirectness) as detailed in Table 7 below.

Table 7: Rationale for downgrading quality of evidence for diagnostic questions

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias.
Indirectness	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level.

GRADE criteria	Reasons for downgrading quality
	Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between direct and indirect studies.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded. Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level. Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies with the smallest and largest effect sizes.
Imprecision	If the 95% confidence interval for a positive likelihood ratio spanned 2, the outcome was downgraded one level, as the data were deemed to be consistent with a meaningful increase in risk and no meaningful predictive value. Similarly, negative likelihood ratios that spanned 0.5 led to downgrading for serious imprecision. Any likelihood ratios that spanned both 0.5 and 2 were downgraded twice, as suffering from very serious imprecision. Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.

The quality of evidence for each outcome was upgraded if either of the following conditions were met:

- Data showing an effect size sufficiently large that it cannot be explained by confounding alone.
- Data where all plausible residual confounding is likely to increase our confidence in the effect estimate.

Publication bias

Publication bias was assessed in two ways. First, if evidence of conducted but unpublished studies was identified during the review (e.g. conference abstracts or protocols without accompanying published data), available information on these unpublished studies was reported as part of the review. Secondly, where 10 or more studies were included as part of a single meta-analysis, a funnel plot was produced to graphically assess the potential for publication bias.

Methods for combining inter-rater agreement evidence

The reliability of agreement for diagnostic data between observers was evaluated using the kappa coefficient. The measure calculates the level of agreement in classification. The

general rule of thumb to follow is: if there is no agreement among the classification, then kappa ≤0; if there is complete agreement then kappa=1 (Fleiss 1971). The following schema (see Table 8), adapted from the suggestions of Fleiss, was used to interpret the level of agreement in diagnostic classification. Random-effects models (der Simonian and Laird) were fitted for all syntheses in R v3.4.0.

In any meta-analyses where some (but not all) of the data came from studies at high risk of bias, a sensitivity analysis was conducted, excluding those studies from the analysis. Results from both the full and restricted meta-analyses are reported. Similarly, in any meta-analyses where some (but not all) of the data came from indirect studies, a sensitivity analysis was conducted, excluding those studies from the analysis.

Table 8: Interpretation of kappa coefficient

Value of kappa coefficients	Interpretation
$\kappa < 0$	No agreement
$0 < \kappa \leq 0.2$	Poor agreement
$0.2 < \kappa \leq 0.4$	Fair agreement
$0.4 < \kappa \leq 0.7$	Good agreement
$0.7 < \kappa < 1.0$	Excellent agreement
$\kappa = 1.0$	Complete agreement

Modified GRADE for inter-rater agreement evidence

GRADE has not been developed for use with inter-rater agreement; therefore a modified approach was applied using the GRADE framework. Data from all study types was initially rated as high quality, with the quality of the evidence for each outcome then downgraded or not from this initial point.

Table 9: Rationale for downgrading evidence for inter-rater agreement

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias.
Inconsistency	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels.

GRADE criteria	Reasons for downgrading quality
	Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between direct and indirect studies.
Indirectness	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded. Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level. Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies with the smallest and largest effect sizes.
Imprecision	If the 95% confidence interval for the kappa coefficient spanned two of the categories in Table 8, it was downgraded one level. If the 95% confidence interval for the kappa coefficient spanned three or more of the categories in Table 8, it was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.

Appendix C – Literature search strategies

Search summary

The search strategies are based on the review protocol provided. The MRI/biopsy terms have been taken from the search strategy used in CG175.

Clinical searches

Source searched for this review question:

- Cochrane Database of Systematic Reviews – CDSR (Wiley)
- Cochrane Central Register of Controlled Trials – CENTRAL (Wiley)
- Database of Abstracts of Reviews of Effects – DARE (Wiley)
- Health Technology Assessment Database – HTA (Wiley)
- EMBASE (Ovid)
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)

The clinical searches were conducted in January 2018.

The MEDLINE search strategy is presented below. It was translated for use in all other databases.

Database: Ovid MEDLINE(R)
1 exp Prostatic Neoplasms/
2 Prostatic Intraepithelial Neoplasia/
3 (prostat* adj4 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcino* or leiomyosarcoma* or lump*)).tw.
4 PIN.tw.
5 or/1-4
6 *Magnetic Resonance Imaging/
7 (magnet* adj2 (resonance* or imag* or scan* or spectroscop*)).tw.
8 (MR adj2 (resonance* or imag* or scan* or spectroscop*)).tw.
9 (Dynamic contrast* enhanc* adj2 (MR* or magnet*)).tw.
10 (contrast* adj2 (imag* or scan*)).tw.
11 ((MRI or MRSI or MP-MR* or MPMR*) adj4 prostat*).tw.
12 turbo spin echo*.tw.
13 ((diffusion* or weight*) adj2 imag*).tw.
14 ((DWI or DCE-MRI or T2W or TSE or T2-weighted MRI*) adj4 prostat*).tw.
15 (Multi-parametric or multiparametric* or biparametric* or bi-parametric*).tw.
16 *biopsy/ or *image-guided biopsy/
17 ((transrectal* or trans-rectal* or transperineal* or trans-perineal*) adj2 (ultrasound* or biops*)).tw.
18 ((saturat* or extend* or templat*) adj2 (ultrasound* or biops*)).tw.
19 ((TRUS or TRUSB) adj4 prostat*).tw.

Database: Ovid MEDLINE(R)	
20	or/6-19
21	5 and 20

Study design filters and limits

A diagnostic filter was appended to the review question above. The MEDLINE filter is presented below. It were translated for use in the MEDLINE In-Process and Embase databases.

An English language limit has been applied.

A date limit from 2007 was applied as the committee members were confident we would unlikely find studies on MRI guided biopsy prior to 2007 that reflect current practice.

Animal studies and certain publication types (letters, historical articles, comments, editorials, news and case reports) have been excluded.

The MEDLINE diagnostic filter	
1	(sensitiv: or diagnos:).mp. or di.fs.
2	Prostate/dg or Prostatic Neoplasms/dg
3	or/1-3

Health Economics search strategy

Economic evaluations and quality of life data.

Sources searched:

- NHS Economic Evaluation Database – NHS EED (Wiley) (legacy database)
- Health Technology Assessment (HTA Database)
- EconLit (Ovid)
- Embase (Ovid)
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)

Search filters to retrieve economic evaluations and quality of life papers were appended to population search terms in MEDLINE, MEDLINE In-Process and Embase to identify relevant evidence and can be seen below.

An English language limit has been applied.

A date limit from 2007 was applied as the committee members were confident we would unlikely find studies on MRI guided biopsy prior to 2007 that reflect current practice.

Animal studies and certain publication types (letters, historical articles, comments, editorials, news and case reports) have been excluded.

The economic searches were conducted in February 2018.

Health Economics filters

The MEDLINE economic evaluations and quality of life search filters are presented below. They were translated for use in the MEDLINE In-Process and Embase databases.

Economic evaluations

1 Economics/
2 exp "Costs and Cost Analysis"/
3 Economics, Dental/
4 exp Economics, Hospital/
5 exp Economics, Medical/
6 Economics, Nursing/
7 Economics, Pharmaceutical/
8 Budgets/
9 exp Models, Economic/
10 Markov Chains/
11 Monte Carlo Method/
12 Decision Trees/
13 econom$.tw.
14 cba.tw.
15 cea.tw.
16 cua.tw.
17 markov$.tw.
18 (monte adj carlo).tw.
19 (decision adj3 (tree$ or analys$)).tw.
20 (cost or costs or costing$ or costly or costed).tw.
21 (price$ or pricing$).tw.
22 budget$.tw.
23 expenditure$.tw.
24 (value adj3 (money or monetary)).tw.
25 (pharmacoeconomic$ or (pharmaco adj economic$)).tw.
26 or/1-25

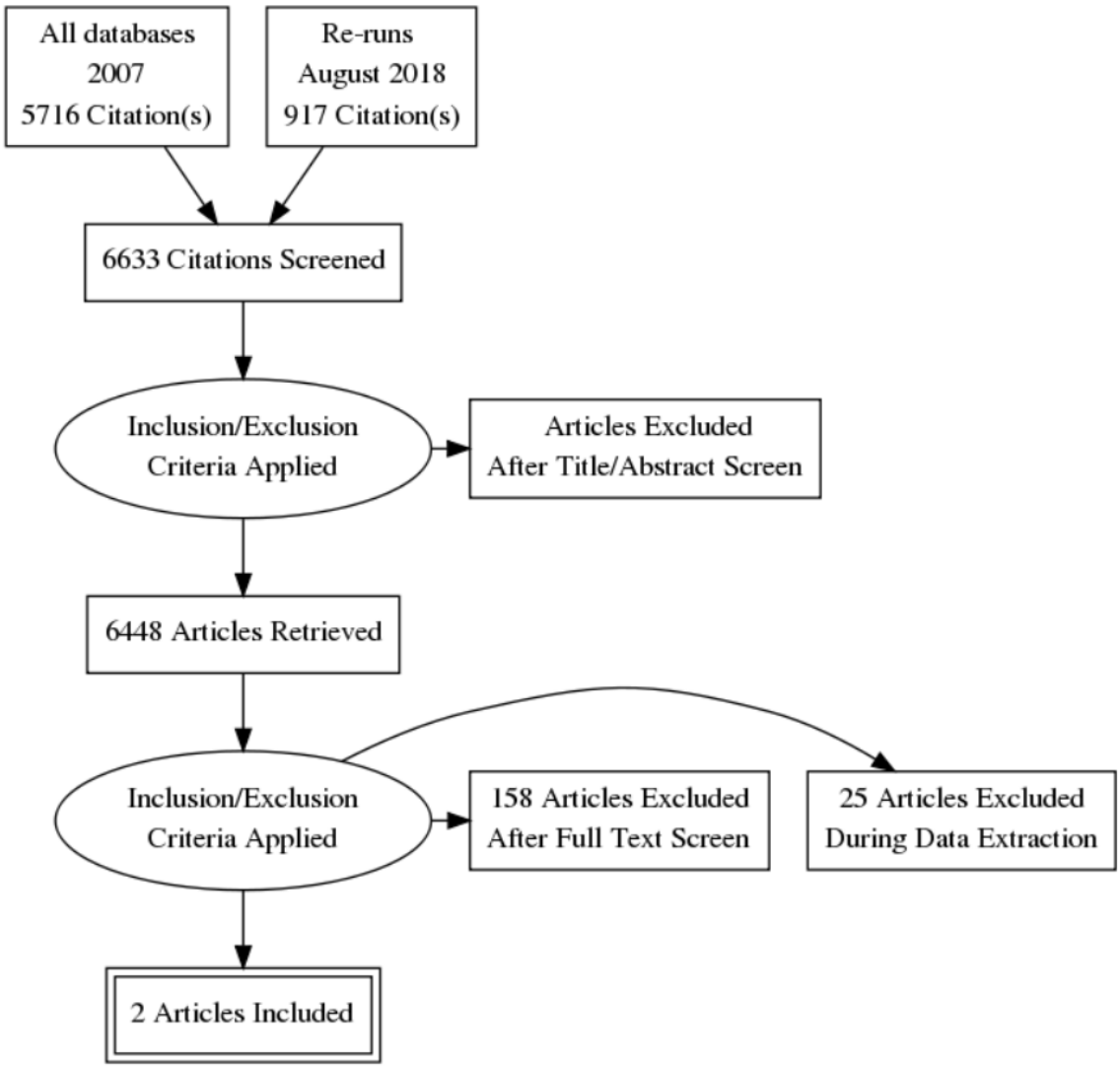
Quality of life

1 "Quality of Life"/
2 quality of life.tw.
3 "Value of Life"/
4 Quality-Adjusted Life Years/
5 quality adjusted life.tw.
6 (qaly$ or qald$ or qale$ or qtime$).tw.
7 disability adjusted life.tw.
8 daly$.tw.
9 Health Status Indicators/
10 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
11 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
12 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
13 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.

The MEDLINE economic evaluations and quality of life search filters are presented below. They were translated for use in the MEDLINE In-Process and Embase databases.
14 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
15 (euroqol or euro qol or eq5d or eq 5d).tw.
16 (qol or hql or hqol or hrqol).tw.
17 (hye or hyes).tw.
18 health$ year$ equivalent$.tw.
19 utilit$.tw.
20 (hui or hui1 or hui2 or hui3).tw.
21 disutili$.tw.
22 rosser.tw.
23 quality of wellbeing.tw.
24 quality of well-being.tw.
25 qwb.tw.
26 willingness to pay.tw.
27 standard gamble$.tw.
28 time trade off.tw.
29 time tradeoff.tw.
30 tto.tw.
31 or/1-30

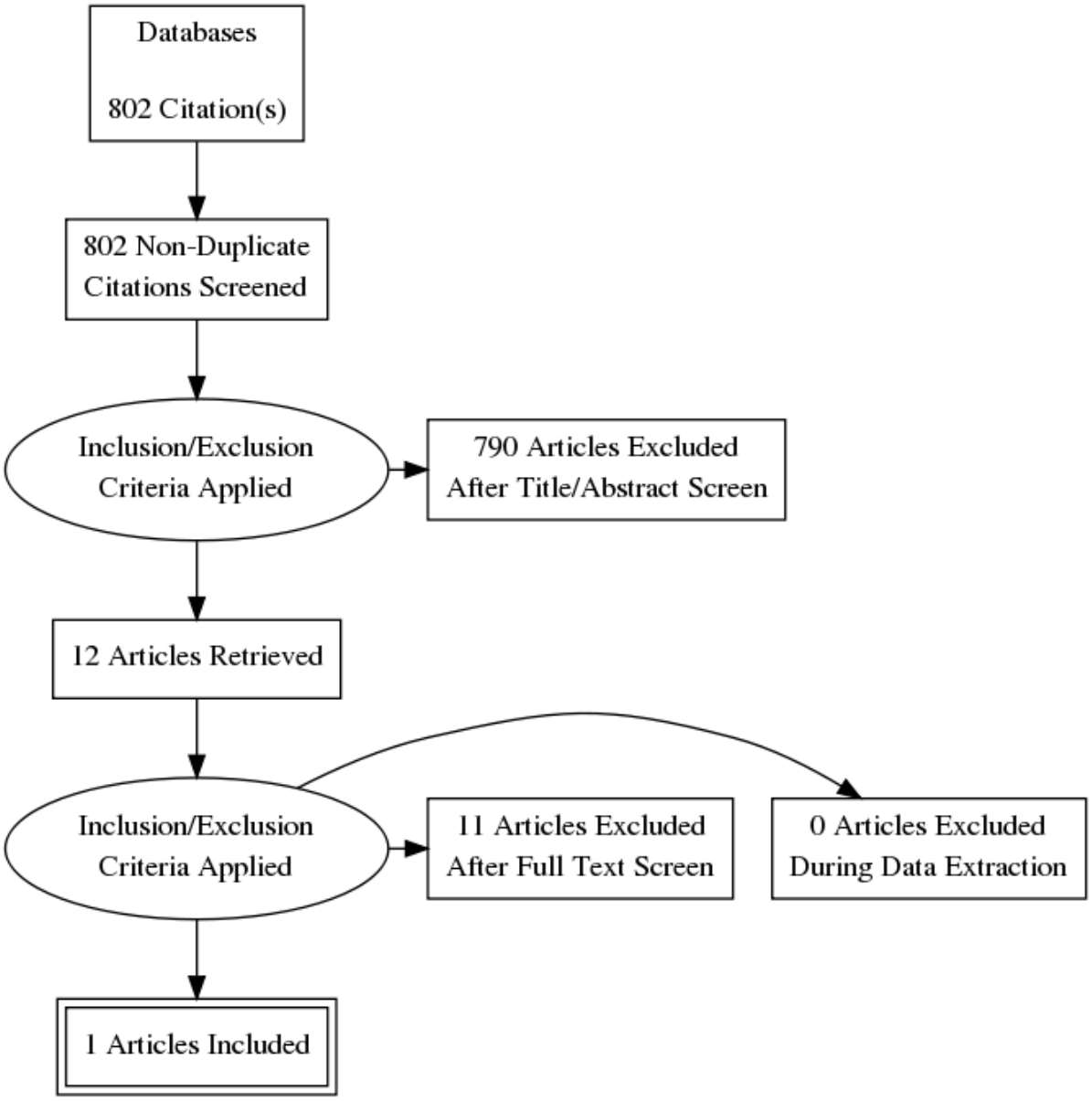
Appendix D – Clinical evidence study selection

Clinical evidence – Diagnostic Cross sectional studies



Clinical evidence - Randomised control studies

Economic evidence



Appendix E – evidence tables

Clinical evidence tables

Diagnosing prostate cancer in people suspected to have prostate cancer (diagnostic cross-sectional studies)

Studies on Multiparametric MRI compared to Transperineal Template Biopsy

Short title	Title	Study Characteristics	Quality Assessment
Ahmed (2017)	Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study	**Study type** Prospective cohort study **Study details** Study location *United Kingdom* Study setting *Hospital* Study dates *May 2012 and November 2015* Sources of funding *Department of Health, National Institute of Health Research - Health Technology Assessment Programme, also partly funded by UCLH/UCL Biomedical Research Centre and the Royal Marsden and Institute for cancer Research*	**Patient selection** Unclear risk of bias *Sampling details were not provided* **Index test** Low risk of bias *Both index tests were interpreted without the knowledge of the results of the reference. The results of the reference and index test were blinded to both the physicians and patients. A threshold was used however it is unclear if this was predefined* **Reference standard** Low risk of bias

Short title	Title	Study Characteristics	Quality Assessment
		Biomedical Research centre **Inclusion criteria** Suspicion of prostate cancer An elevated serum PSA (up to 15 ng/ml) within previous 3 months Suspicious digital rectal examination Suspected organ confined stage T2 or lower on rectal examination Family history Aged at least 18 years Fit for general or spinal anaesthesia All protocol procedures including a transrectal ultrasound **Exclusion criteria** Previous treatment for prostate cancer If they were using 5-alpha-reductase inhibitors at time of registration or during the previous 6 months Previous history of prostate biopsy Prostate surgery Had evidence of urinary tract infection History of acute prostatitis within the last 3 months Had any contraindication to MRI (eg,	*The reference standard was chosen by the committee and regarded as gold standard* **Flow and timing** Low risk of bias *"TRUS biopsy was performed straight after transperineal biopsy under the same general anaesthetic". It is unclear when the MP-MRI was carried in relation to the reference standard* **Overall risk of bias** Low **Directness** Directly applicable

Short title	Title	Study Characteristics	Quality Assessment
		claustrophobia, pacemaker, estimated glomerular filtration rate </=50) Had any other medical condition precluding procedures described in the protocol Had previous history of hip replacement surgery, metallic hip replacement or extensive pelvic orthopaedic metal work **Sample characteristics** Sample size *576 patients* Mean age (SD) *63.4 years (7.6)* Mean PSA ng/ml *7.1 ng/ml SD (2.9) (range 0.5 to 15)* **Index test(s)** Multiparametric MRI TRUS biopsy **Reference standard(s)** Transperineal prostate biopsy	

Short title	Title	Study Characteristics	Quality Assessment
Nafie (2014)	The role of transperineal template prostate biopsies in prostate cancer diagnosis in biopsy naive men with PSA less than 20 ng ml^{-1}	**Study type** Prospective cohort study **Study details** Study location *UK* Study setting *hospital* Study dates *August 2012 and August 2013* Sources of funding *not stated* **Inclusion criteria** Benign feeling prostate on DRE and elevated serum PSA <20ng/ml **Exclusion criteria** None reported **Sample characteristics** Sample size *50 patients*	**Patient selection** Unclear risk of bias *No details were provided on the sampling technique of the study participants. The study was not of a case control design, all patients had both tests done. The authors did not state any exclusion criteria* **Index test** Unclear risk of bias *Both tests were carried out at the same time, however the same pathologists interpreted both histological analysis - it is therefore unclear if the index tests were interpreted prior to the reference standard results.* **Reference standard** Low risk of bias *The reference standard was chosen by the committee and was regarded as gold standard* **Flow and timing** Low risk of bias

Short title	Title	Study Characteristics	Quality Assessment
		Mean age (SD) *median age - 67 years (range 54-84)* Mean prostate volume (sd) *58cc (range 19-165)* Mean PSA ng/ml *8ng/ml (range 4-18)* **Index test(s)** TRUS biopsy **Reference standard(s)** Transperineal prostate biopsy	*Both tests were done simultaneously* **Overall risk of bias** Moderate *Due to uncertainties surrounding patient section and whether or not the index tests results were interpreted without the knowledge of reference standard* **Directness** Directly applicable

Diagnosing prostate cancer in people suspected to have prostate cancer (RCTs)

Short title	Title	Study Characteristics	Quality Assessment
Kasivisvanathan (2018)	MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis.	**Study type** Randomised controlled trial **Study details** Study location *25 centres in 11 countries* Study dates *February 2016 - August 2017*	**Random sequence generation** Low risk of bias **Allocation concealment** Low risk of bias

Short title	Title	Study Characteristics	Quality Assessment
		Duration of follow-up *Until visit when treatment decisions were made or until 30-day post intervention questionnaires completed (whichever was later).* Sources of funding *National Institute for Health Research and the European Association of Urology Research Foundation* **Inclusion criteria** Abnormal Digital Rectal Examination No previous prostate biopsy High PSA levels *Elevated PSA level* PSA <20 ng/ml or free-to-total PSA ration <0.15 and <10 ng/ml in repeated measurements Negative digital rectal exam **Exclusion criteria** None reported **Sample characteristics** Sample size *500*	**Blinding of participants and personnel** Low risk of bias **Blinding of outcome assessment** Unclear risk of bias *Quantitative data have low risk of bias. Higher risk for participant's follow up questionnaires.* **Incomplete outcome data** Low risk of bias **Selective reporting** Low risk of bias **Other sources of bias** Low risk of bias **Overall risk of bias** Low

Short title	Title	Study Characteristics	Quality Assessment
		Split between study groups *MRI-targeted biopsy group v standard biopsy group.* Mean age (SD) *MRI-targeted biopsy group: 64.4 (7.5) Standard biopsy group: 64.5 (8.0)* Mean PSA (ng/ml) *Median (IQR) MRI-targeted biopsy group: 6.75 (5.16 - 9.35) Standard biopsy group: 6.50 (5.14 - 8.65)* Abnormal finding on DRE *MRI-targeted biopsy group: 36% (14) Standard biopsy group: 38% (15)* Family history of prostate cancer (%) *MRI-targeted biopsy group: 48 (19) Standard biopsy group: 40 (16)* **Interventions** MRI-targeted TRUS biopsy v TRUS biopsy alone **Outcome measure(s)** Proportion of men with clinically significant prostate cancer *Biopsy core with Gleason score of 3+4 (Gleason sum of 7) or greater.* Complications that occurred	**Directness** Directly applicable

Short title	Title	Study Characteristics	Quality Assessment
		Proportion of men with adverse effects after intervention. Proportion of men with clinically insignificant prostate cancer *Gleason score 3+3* Proportion of men who did not undergo biopsy after MRI	
Porpiglia (2017)	Diagnostic Pathway with Multiparametric Magnetic Resonance Imaging Versus Standard Pathway: Results from a Randomized Prospective Study in Biopsy-naive Patients with Suspected Prostate Cancer	**Study type** Randomised controlled trial **Study details** Study location *Italy* Study setting *Ambulatory care* Study dates *November 2014 - March 2016* **Inclusion criteria** Aged less than 75 PSA <15 ng/ml Negative digital rectal exam	**Random sequence generation** Low risk of bias **Allocation concealment** Low risk of bias **Blinding of participants and personnel** Low risk of bias **Blinding of outcome assessment** Low risk of bias **Incomplete outcome data** Low risk of bias

Short title	Title	Study Characteristics	Quality Assessment
		Exclusion criteria Previous prostate biopsy or MRI of prostate Contraindication to MRI **Sample characteristics** Sample size *212* Split between study groups Control *Standard prostate biopsy* Intervention *mpMRI prior to prostate biopsy* Mean age (SD) *mpMRI group: 64 (58 - 70) Control group: 66 (60 - 70)* Mean PSA (ng/ml) *Median (IQR) mpMRI group: 5.9 (4.8 - 7.5)* *Control group: 6.7 (5.5 - 8.5)* Mean Prostate Volume (ml) *Median (IQR) mpMRI group: 46.2 (34.5 - 71.6)* *Control group: 45.7 (34.6 - 65.0)* **Split between study groups** Control *Standard prostate biopsy*	**Selective reporting** Low risk of bias **Other sources of bias** Low risk of bias **Overall risk of bias** Low **Directness** Directly applicable

Short title	Title	Study Characteristics	Quality Assessment
		Intervention *mpMRI prior to prostate biopsy* **Interventions** MRI-targeted TRUS biopsy v TRUS biopsy alone **Outcome measure(s)** Cancer detection rate	

Health economics

Study, population, country and quality	Data sources	Other comments	Strategy*	Total Cost (£)	Total Effect (QALYs)	Total ICER (£/QALY)	Authors' conclusions	Uncertainty
PROMIS- Faria et al. 2018 Biopsy-naïve men > 18 year-old at risk of PC, advised	<u>Effectiveness:</u> Diagnostic accuracy data affecting the number of cancer detected, of biopsies spared, overall survival,	Decision tree for the short-term diagnostic data from PROMIS and Markov model for the long-term outcome, capturing lifetime costs and health benefits from using 383 different strategies of PC diagnosis, including up to 3 techniques: TRUS, MRI	Base case				Based on the more sensitive definitions of CS PC, Introducing MP-MRI first then up to two MRI-	Results are sensitive to the costs of diagnostics and sensitivity of MRI-targeted TRUS. Reducing this
			T7 223	5,194	8.69	-		
			M7 222	5,367	8.72	7,076		
			P4 2-- [t]	5,968	8.74	30,084		

Study, population, country and quality	Data sources	Other comments	Strategy*	Total		ICER (£/QALY)	Authors' conclusions	Uncertainty
				Cost (£)	Effect (QALYs)			
to prostate biopsy, PSA <= 15 ng/ml within the previous 3 months, prostate volume < 100cc, referred to secondary care for further investigation A UK study **Directly applicable** **Minor limitations** [a, b, c]	PC-specific death and time to progression Cost: £ 2015 prices, NHS and PSS perspective Utility: Disutility from experiencing the TPMB (short-term), aging and metastases (long-run) obtained from patient reported EQ5D in PROMIS and identified from literature	and TPM with different possible sequences, two definitions for CS PC using TRUS and MP-MRI, and different cut-offs for MP-MRI to be positive. Reference test is combining TRUS and TPM whichever is more severe. IPD from PROMIS bootstrapped 1000 times to include accuracy data as probability dist. False negative cases were assigned the progression/mortality rate obtained from the active surveillance arm in PIVOT. These cases were not identified later, as the model did not consider re-testing Probabilities of progression and mortality in the long-run, assumed constant, were derived by state transition model calibration based on cumulative incidence of metastases and death reported at specific time intervals in published clinical trials.					targeted TRUS appeared to be cost-effective at cost-effectiveness thresholds up to 30k/QALY	sensitivity resulted in strategies beginning with TRUS being cost-effective; those with negative results receive MP-MRI and then the positive cases undergo MRI-targeted TRUS.

Study, population, country and quality	Data sources	Other comments	Strategy*	Total		ICER (£/QALY)	Authors' conclusions	Uncertainty
				Cost (£)	Effect (QALYs)			
a) Techniques used in MRI-targeted TRUS not specified b) Uncertainty around the sensitivity of MRI-targeted biopsy c) Uncertainty in the long-run outcome related to progression rate estimated for the diagnosed and misclassified cases * T7: starting by all patients receive TRUS; cases with no cancer or CNS cancer receive MP-MRI; those with suspicion of CS cancer undergo 2nd TRUS. M7: starting by all patients receive MP-MRI; those with suspicion of CS cancer undergo TRUS; cases with no cancer or CNS cancer receive 2nd TRUS. P4: starting by all patients receive TRUS; cases with no cancer or CNS cancer receive 2nd TRUS. 223/222: 1st digit: secondary TRUS definition of CS PC (Gleason >/=3+4 and/or cancer core length >/=4mm); 2nd digit: secondary MP-MRI definition of CS PC (volume >0.2cc and/or Gleason >/=3+4); 3rd digit: MP-MRI cut-off (based on Likert score from 1 to 5) t: this strategy does not include MP-MRI								

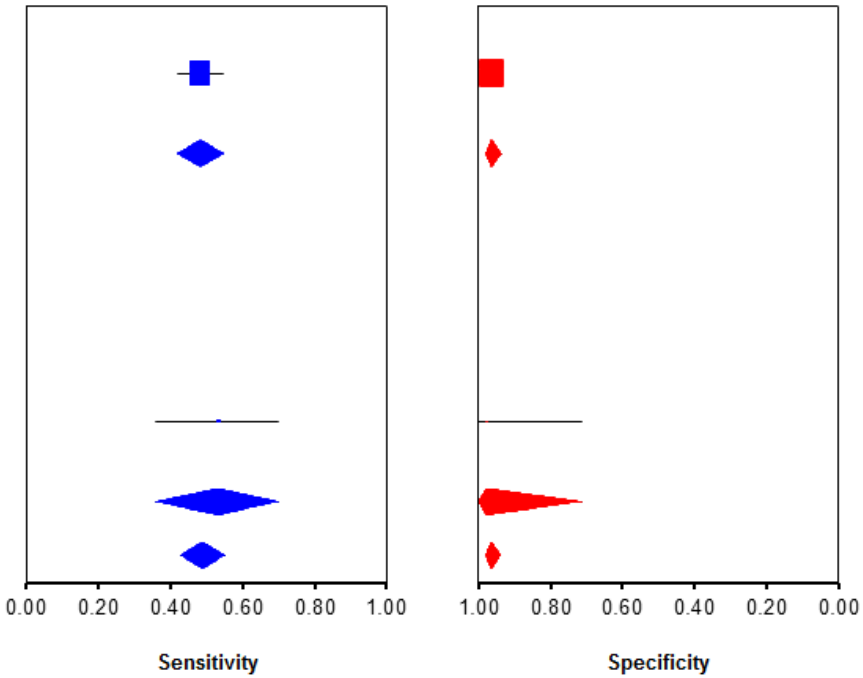
Appendix F – Forest plots

Diagnosing prostate cancer in people suspected to have prostate cancer – cross-sectional studies

TRUS biopsy compared to Transperineal Template Biopsy – Sensitivity and specificity for clinically significant cancer

Study	TP	FN	FP	TN	Sens. (95%CI)	Spec. (95%CI)
Definition of clin. sig. cancer: UCL1						
Per patient						
Ahmed (2017)	111	119	13	333	0.48 (0.42, 0.55)	0.96 (0.94, 0.98)
Per sector						
no data						
RE subtotal					**0.48 (0.42, 0.55)**	**0.96 (0.94, 0.98)**
Definition of clin. sig. cancer: any Gleason 7+						
Per patient						
no data						
Per sector						
no data						
Definition of clin. sig. cancer: any cancer						
Per patient						
Nafie (2014)	16	14	0	20	0.53 (0.36, 0.70)	0.98 (0.71, 1.00)
Per sector						
no data						
RE subtotal					**0.53 (0.36, 0.70)**	**0.98 (0.71, 1.00)**
RE meta-analysis					**0.49 (0.43, 0.55)**	**0.96 (0.94, 0.98)**

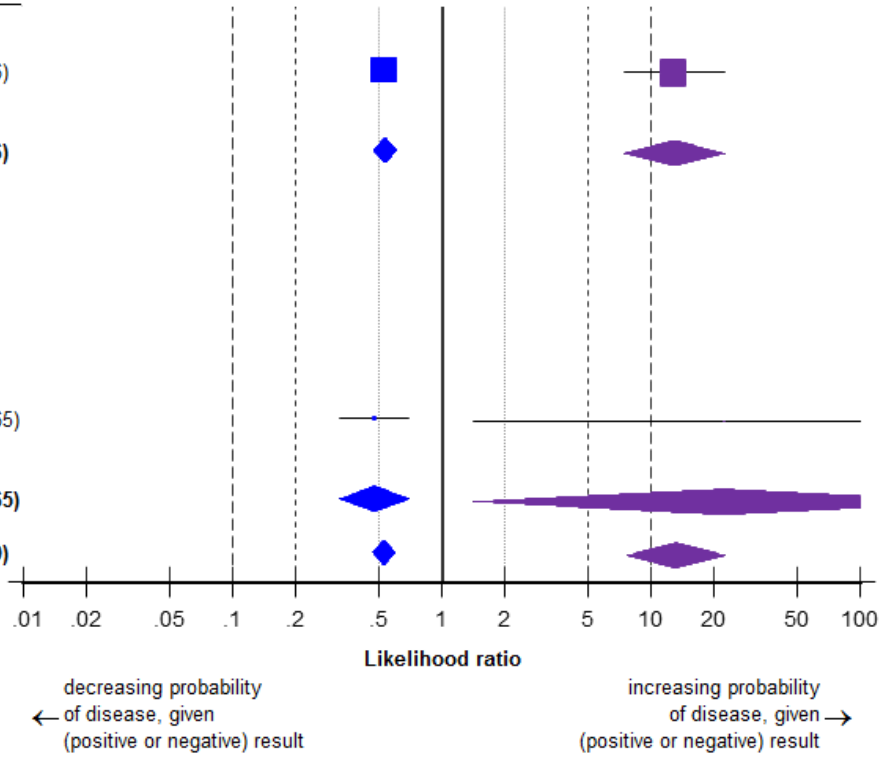
Overall heterogeneity, sens: Tau²=0.00; Chi²=0.27, df=1 (p=0.604); I²=0.0%
Overall heterogeneity, spec: Tau²=0.00; Chi²=0.10, df=1 (p=0.747); I²=0.0%
Between-stratum heterogeneity, sens: Chi²=0.27, df=1 (p=0.604); I²=0.0%
Between-stratum heterogeneity, spec: Chi²=0.10, df=1 (p=0.747); I²=0.0%



TRUS biopsy compared to Transperineal Template Biopsy - Likelihood ratios for clinically significant cancer

Study	TP	FN	FP	TN	LR- (95%CI)	LR+ (95%CI)
Definition of clin. sig. cancer: UCL1						
Per patient						
Ahmed (2017)	111	119	13	333	0.54 (0.47, 0.61)	12.84 (7.41, 22.26)
Per sector						
no data						
RE subtotal					**0.54 (0.47, 0.61)**	**12.84 (7.41, 22.26)**
Definition of clin. sig. cancer: any Gleason 7+						
Per patient						
no data						
Per sector						
no data						
Definition of clin. sig. cancer: any cancer						
Per patient						
Nafie (2014)	16	14	0	20	0.48 (0.33, 0.70)	22.35 (1.42, 352.65)
Per sector						
no data						
RE subtotal					**0.48 (0.33, 0.70)**	**22.35 (1.42, 352.65)**
RE meta-analysis					**0.53 (0.47, 0.60)**	**13.12 (7.65, 22.50)**

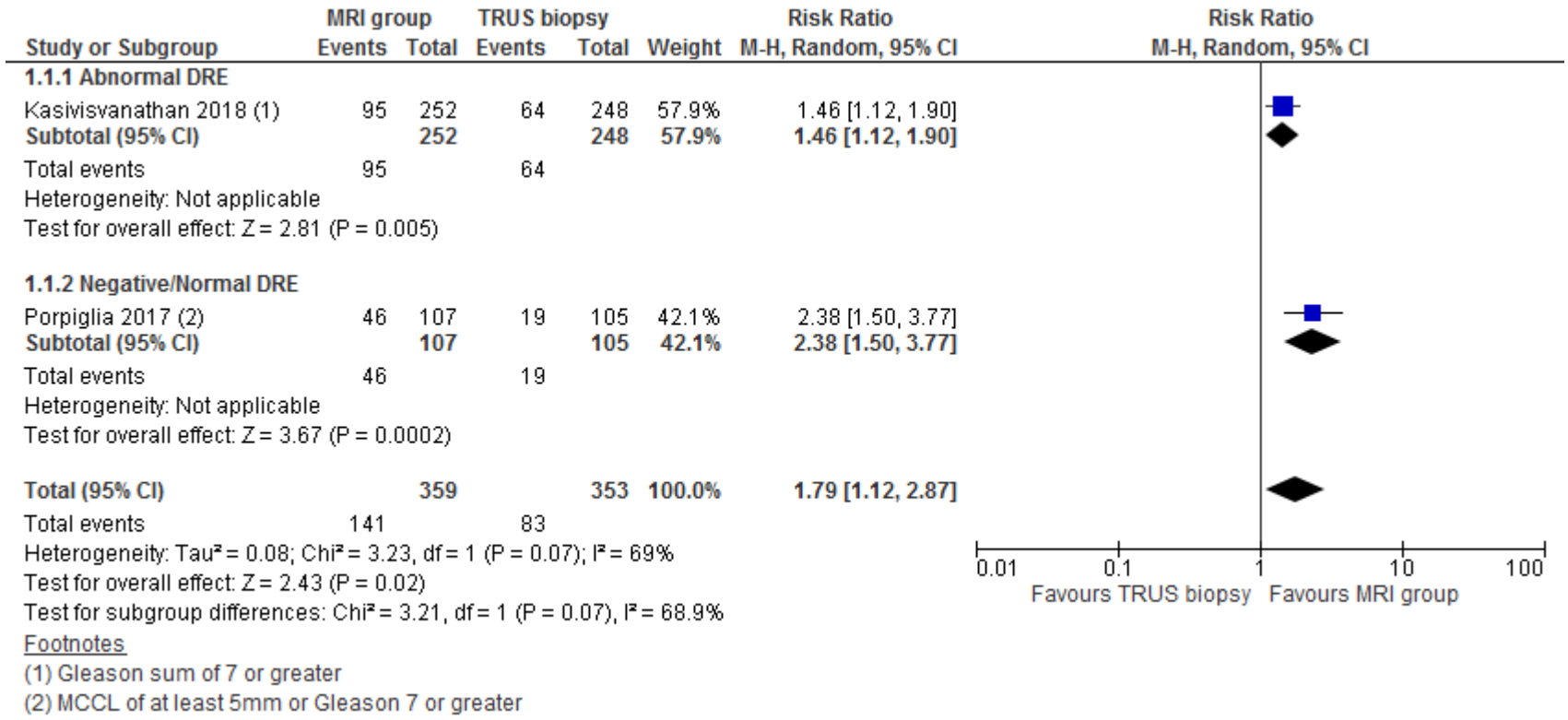
Overall heterogeneity, LR-: Tau²=0.00; Chi²=0.32, df=1 (p=0.575); I²=0.0%
Overall heterogeneity, LR+: Tau²=0.00; Chi²=0.15, df=1 (p=0.699); I²=0.0%
Between-stratum heterogeneity, LR-: Chi²=0.32, df=1 (p=0.575); I²=0.0%
Between-stratum heterogeneity, LR+: Chi²=0.15, df=1 (p=0.699); I²=0.0%



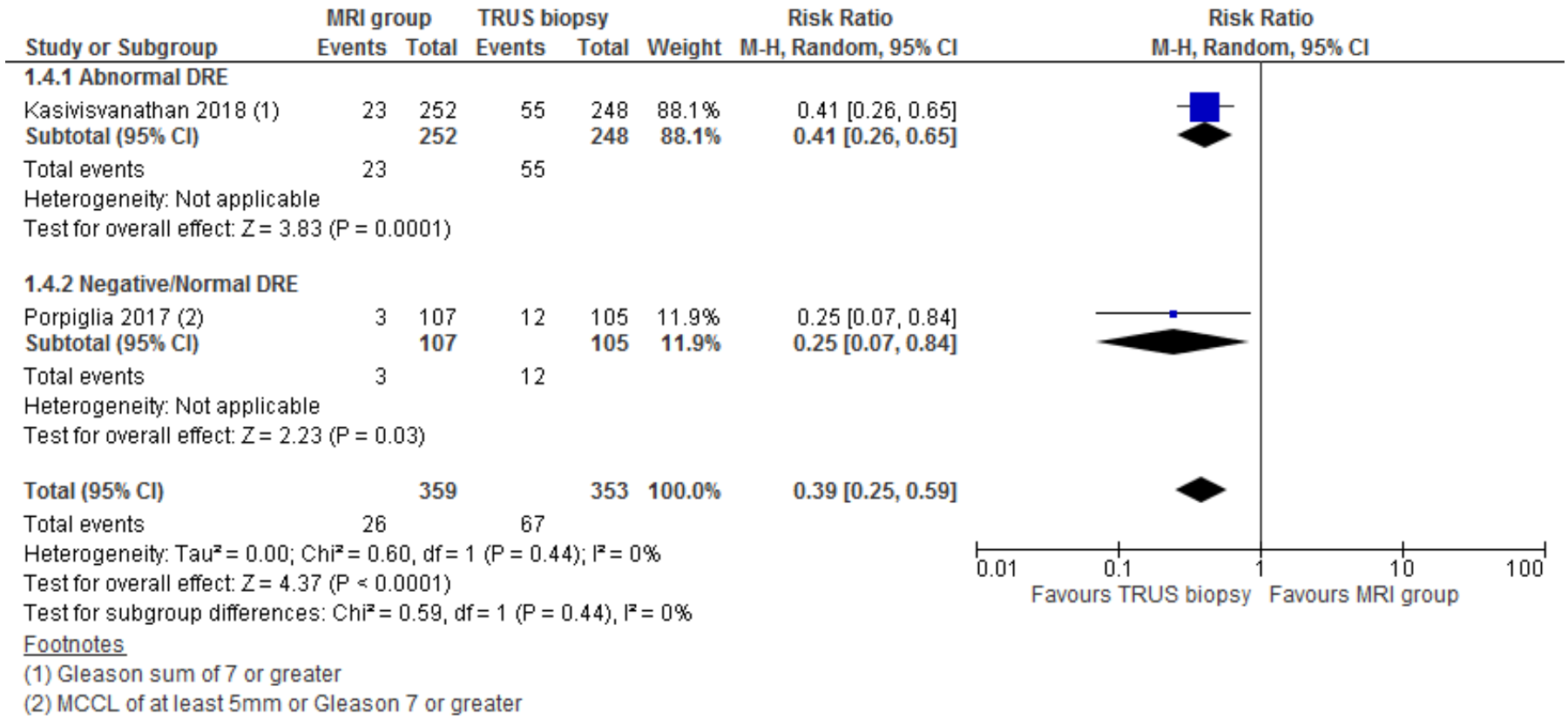
Diagnosing prostate cancer in people suspected to have prostate cancer – randomised control studies

MRI influenced Biopsy versus TRUS biopsy –

Proportion of people with clinically significant cancer



Proportion of people with clinically insignificant cancer

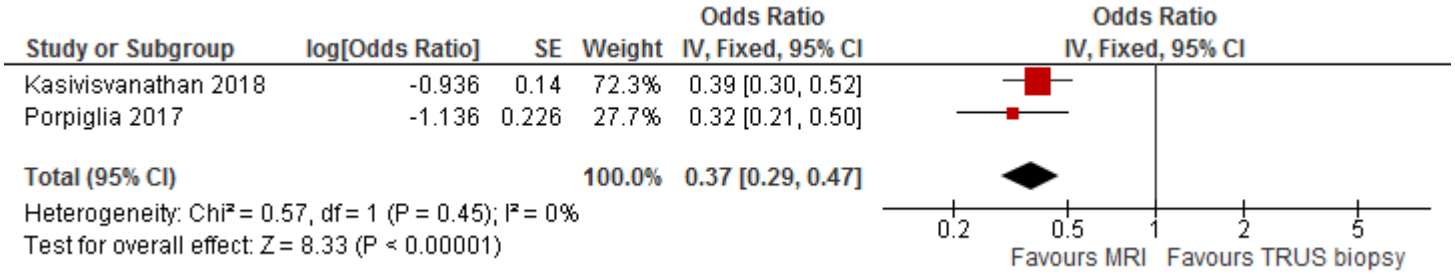


Footnotes

(1) Gleason sum of 7 or greater

(2) MCCL of at least 5mm or Gleason 7 or greater

People who avoided biopsy

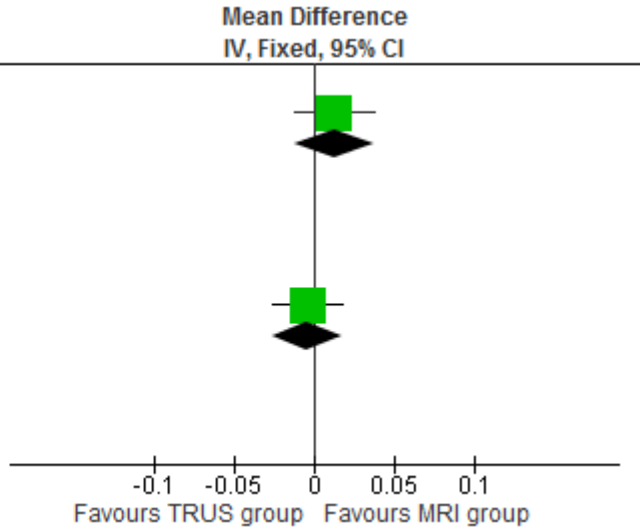


The forest plot shows the odds and not odds ratio – this was converted to the equivalent proportion for easy interpretation and this equates to 0.27 (0.22, 0.31)

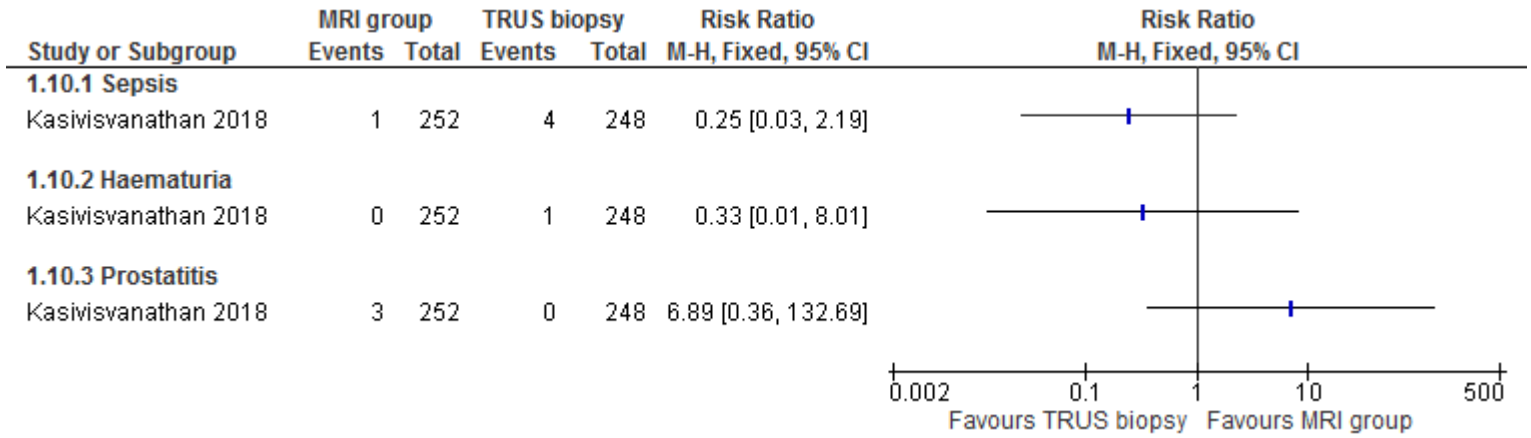
Health related quality of life EQ 5D description

Study or Subgroup	MRI group Mean	SD	Total	TRUS biopsy Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.8.1 24 hours post intervention								
Kasivisvanathan 2018	0.907	0.126	252	0.894	0.159	248	100.0%	0.01 [-0.01, 0.04]
Subtotal (95% CI)			**252**			**248**	**100.0%**	**0.01 [-0.01, 0.04]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.01 (P = 0.31)								
1.8.2 30 days post intervention								
Kasivisvanathan 2018	0.917	0.124	252	0.921	0.126	248	100.0%	-0.00 [-0.03, 0.02]
Subtotal (95% CI)			**252**			**248**	**100.0%**	**-0.00 [-0.03, 0.02]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.36 (P = 0.72)								

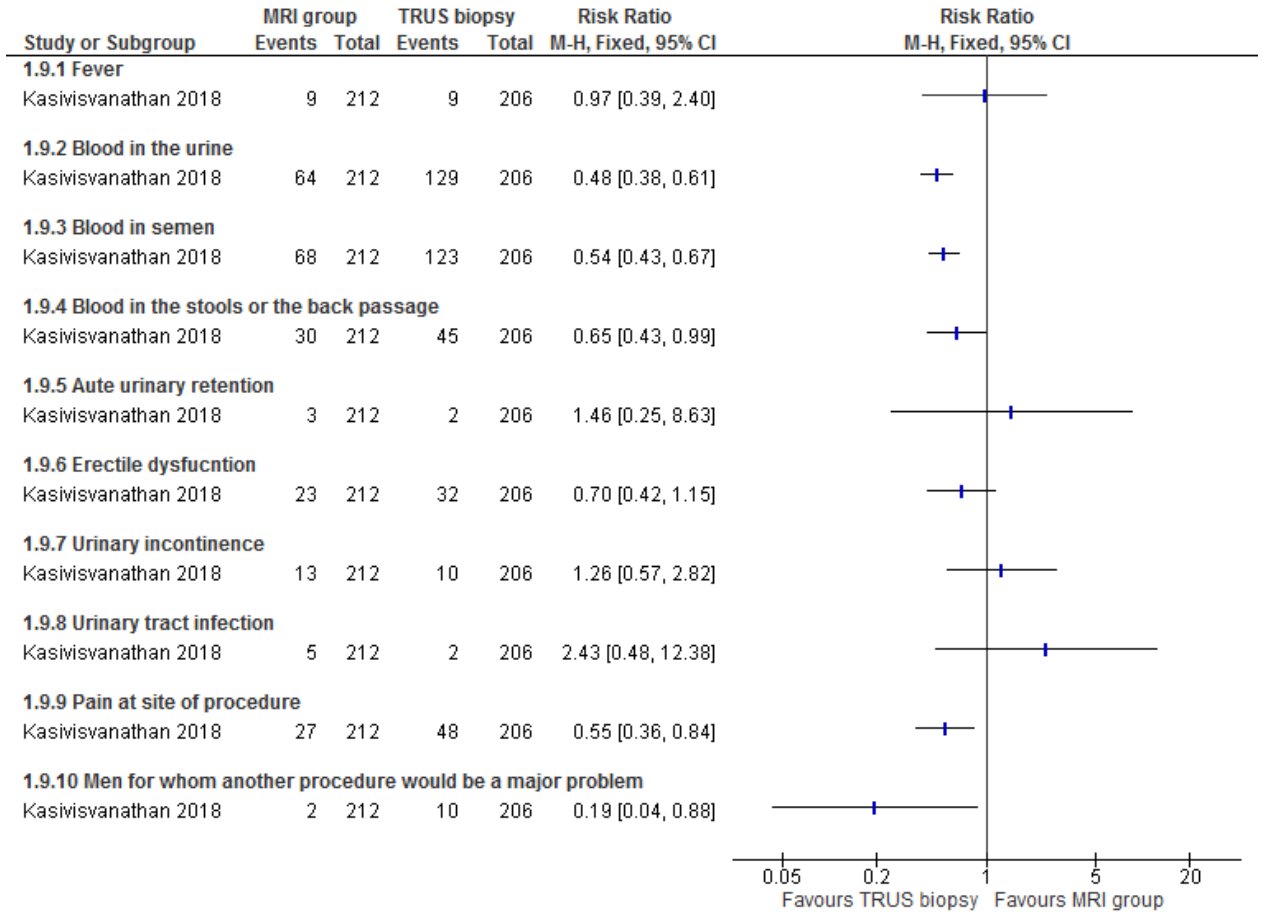
Test for subgroup differences: Chi² = 1.00, df = 1 (P = 0.32), I² = 0%



Investigator reported adverse events related to the interventions


MRI group
TRUS biopsy
Risk Ratio
Risk Ratio
Study or Subgroup
Events Total Events Total M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
1.10.1 Sepsis
Kasivisvanathan 2018 1 252 4 248 0.25 [0.03, 2.19]
1.10.2 Haematuria
Kasivisvanathan 2018 0 252 1 248 0.33 [0.01, 8.01]
1.10.3 Prostatitis
Kasivisvanathan 2018 3 252 0 248 6.89 [0.36, 132.69]
0.002
0.1
1
10
500
Favours TRUS biopsy
Favours MRI group

Patient reported 30 day post intervention complications



Appendix G – GRADE tables

Diagnosing prostate cancer in people suspected to have prostate cancer (diagnostic cross-sectional studies)

Multiparametric MRI

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Multiparametric MRI - (reference standard: transperineal template mapping biopsy) analysis by person, MRI threshold ≥2										
1 study Ahmed (2017)	Prospective cross sectional study	576	0.98 (0.96, 0.99)	0.07 (0.05, 0.11)	LR- 0.26 (0.11, 0.65)	Not serious	N/A	Not serious	Not serious	High
					LR+ 1.06 (1.02, 1.10)	Not serious	N/A	Not serious	Not serious	High
Multiparametric MRI - (reference standard: transperineal template mapping biopsy) analysis by person, MRI threshold ≥3										
1 study Ahmed (2017)	Prospective cross sectional study	576	0.93 (0.88, 0.95)	0.41 (0.36, 0.46)	LR- 0.18 (0.11, 0.29)	Not serious	N/A	Not serious	Not serious	High
					LR+ 1.56 (1.42, 1.72)	Not serious	N/A	Not serious	Not serious	High
Multiparametric MRI - (reference standard: transperineal template mapping biopsy) analysis by person, MRI threshold ≥4										
1 study Ahmed (2017)	Prospective cross sectional study	576	0.68 (0.62, 0.73)	0.86 (0.81, 0.89)	LR- 0.38 (0.32, 0.45)	Not serious	N/A	Not serious	Not serious	High
					LR+ 4.70 (3.44, 6.42)	Not serious	N/A	Not serious	Not serious	High
Multiparametric MRI - (reference standard: transperineal template mapping biopsy) analysis by person, MRI threshold of 5										
1 study	Prospective cross-	576	0.40 (0.35, 0.52)	0.97 (0.94, 0.99)	LR- 0.62 (0.57, 0.68)	Not serious	N/A	Not serious	Not serious	High

Ahmed (2017)	sectional study				LR+ 14.25 (6.78, 29.95)	Not serious	N/A	Not serious	Not Serious	High

TRUS biopsy

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
TRUS biopsy - (reference standard: transperineal template mapping biopsy) analysis by person										
2 studies Ahmed (2017) Nafie (2014)	Prospective cross sectional study	626	0.49 (0.43, 0.55)	0.96 (0.94, 0.98)	LR- 0.53 (0.47, 0.82)	Not serious	Not serious	Not serious	Serious[1]	Moderate
					LR+ 13.12 (7.65, 22.50)	Not serious	Not serious	Not serious	Not serious	High
Definition of clinically significant cancer - UCL definition 1: Gleason ≥4+3 and/or maximum cancer core length (CCLmax) ≥6mm										
1 study Ahmed (2017)	Cross sectional study	576	0.44 (0.30, 0.59)	0.96 (0.94, 0.98	LR- 0.54 (0.47, 0.61)	Not serious	N/A	Not serious	Serious[1]	Moderate
					LR+ 12.84 (7.41, 22.26)	Not serious	N/A	Not serious	Not serious	High
Definition of clinically significant cancer - Any cancer										
1 study Nafie (2014)	Cross sectional study	50	0.53 (0.36, 0.70)	0.98 (0.71, 1.00)	LR- 0.60 (0.44, 0.82)	Serious[2]	N/A	Not serious	Serious	Low
					LR+ 12.34 (7.32, 20.80)	Serious[2]	N/A	Not serious	Not serious	Moderate

1. 95% confidence interval for likelihood ratio crosses one end of a defined MID interval – (0.5, 2), downgraded once
2. Moderate risk of bias – due to selection bias – unclear how the study participants were selected, downgraded once

Diagnosing prostate cancer – randomised control trials

MRI influenced prostate biopsy (Targeted biopsy) versus prostate biopsy

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Proportion of people with clinically significant cancer (RR>1 favours MRI group)										
2 Studies Kasivisvanathan (2018) Porpligia (2017)	RCTs	712	RR 1.79 (1.12, 2.87)	23.5 per 100 people	42.1 per 100 people (26.3 Fewer to 67.4 more)	Not serious	Very serious[1]	Not serious	Serious[2]	Very Low
Proportion of people with clinically insignificant cancer (RR>1 favours MRI group)										
2 Studies Kasivisvanathan (2018) Porpligia (2017)	RCTs	712	RR 0.39 (0.25, 0.59)	18.9 per 100 people	7.4 per 100 people (4.73 fewer to 11.2 more)	Not serious	Not Serious	Not serious	Not serious	High
Proportion of people who avoided biopsy										
2 studies Kasivisvanathan (2018) Porpligia (2017)	RCTs	456	0.27 (0.22, 0.31)	-	-	Not serious	Not serious	Not serious	Not serious	High
Health-related quality of life measured by EQ-5D (descriptive score) (MD >0 favours MRI group)										
Score at 24 hours post intervention										
1 study	RCTs	500	MD 0.01 (-0.01. 0.04)	-	-	Not serious	N/A	Not serious	Not serious	High

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Kasivisvanathan (2018)										
Score at 30 days post intervention										
1 study Kasivisvanathan (2018)	RCTs	500	MD 0.00 (-0.03. 0.02)	-	--	Not serious	N/A	Not serious	Not serious	High
Investigator reported adverse event related to the interventions (RR<1 favours MRI group)										
Sepsis										
1 study Kasivisvanathan (2018)	RCTs	500	RR 0.25 (0.03, 2.19)	1.61 per 100 people	11.3 per 100 people (4.27 fewer to 32.5 more)	Not serious	N/A	Not serious	Very Serious[3]	Low
Haematuria										
1 study Kasivisvanathan (2018)	RCTs	500	RR 0.39 (0.01, 8.01)	0.4 per 100 people	0.16 per 100 people (0.004 fewer to 3.2 more)	Not serious	N/A	Not serious	Very Serious[2]	Low
Prostatitis										
1 study Kasivisvanathan (2018)	RCTs	500	RR 6.89 (0.36, 132.86)	No cases in the control group	Unable to calculate	Not serious	N/A	Not serious	Very Serious[3]	Low
Patient reported adverse event related to the interventions (RR<1 favours MRI group)										
Fever										
1 study	RCTs	418	RR 0.97 (0.39, 2.40)	4.37 per 100 people	4.24 per 100 people (1.70	Not serious	N/A	Not serious	Very Serious[3]	Low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Kasivisvanathan (2018)					fewer to 23.8 more)					
Blood in the urine										
1 study Kasivisvanathan (2018)	RCTs	418	RR 0.48 (0.38, 0.61)	62.6 per 100 people	30.1 per 100 people (23.8 fewer to 38.2 more)	Not serious	N/A	Not serious	Not serious	High
Blood in the semen										
1 study Kasivisvanathan (2018)	RCTs	418	RR 0.54 (0.43, 0.67)	59.7 per 100 people	32.2 per 100 people (25.7 fewer to 40.0 more)	Not serious	N/A	Not serious	Not serious	High
Blood in the stools or back passage										
1 study Kasivisvanathan (2018)	RCTs	418	RR 0.65 (0.43, 0.99)	21.8 per 100 people	14.2 per 100 people (9.39 fewer to 21.6 more)	Not serious	N/A	Not serious	Serious[2]	Moderate
Acute urinary retention										
1 study Kasivisvanathan (2018)	RCTs	418	RR 1.46 (0.25, 8.63)	0.97 per 100 people	1.42 per 100 people (0.24 fewer to 8.34 more)	Not serious	N/A	Not serious	Very Serious[3]	Low
Erectile dysfunction										
1 study Kasivisvanathan (2018)	RCTs	418	RR 0.70 (0.42, 1.15)	15.5 per 100 people	10.9 per 100 people (6.52 fewer to 17.9 more)	Not serious	N/A	Not serious	Serious[2]	Moderate

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Urinary incontinence										
1 study Kasivisvanathan (2018)	RCTs	418	RR 1.26 (0.57, 2.82)	4.85 per 100 people	6.12 per 100 people (2.77 fewer to 13.7 more)	Not serious	N/A	Not serious	Very Serious[3]	Low
Urinary tract infection										
1 study Kasivisvanathan (2018)	RCTs	418	RR 2.43 (0.48, 12.38)	0.97 per 100 people	2.36 per 100 people (0.47 fewer to 12.0 more)	Not serious	N/A	Not serious	Very Serious[3]	Low
Pain at site of procedure										
1 study Kasivisvanathan (2018)	RCTs	418	RR 0.55 (0.36, 0.84)	23.3 per 100 people	12.8 per 100 people (8.39 fewer to 19.6 more)	Not serious	N/A	Not serious	Serious[2]	Moderate
Men for whom another procedure would be a major problem										
1 study Kasivisvanathan (2018)	RCTs	418	RR 0.19 (0.04, 0.88)	4.85 per 100 people	0.92 per 100 people (0.19 fewer to 4.27 more)	Not serious	N/A	Not serious	Serious[2]	Moderate

1. I^2 was greater than 66.7%, downgraded twice
2. the 95% confidence interval for the effect size crossed one line of the MID, downgraded once
3. the 95% confidence interval for the effect size crossed both lines of the MIDs, downgraded twice

Appendix H – Excluded studies

Clinical studies

RQ1 Diagnostic cross-sectional studies

Short Title	Title	Reason for exclusion
A'Amar (2013)	Comparison of elastic scattering spectroscopy with histology in ex vivo prostate glands: Potential application for optically guided biopsy and directed treatment	Reference standard in study does not match that specified in protocol
Abd-Alazeez (2014)	Performance of multiparametric MRI in men at risk of prostate cancer before the first biopsy: A paired validating cohort study using template prostate mapping biopsies as the reference standard	Only included population with negative TRUS/MRI results Only included people with overall MRI score ≥3
Abd-Alazeez (2014)	Can multiparametric magnetic resonance imaging predict upgrading of transrectal ultrasound biopsy results at more definitive histology?	Not possible to calculate a 2x2 table from data presented in the study
Abd-Alazeez (2015)	Multiparametric MRI for detection of radiorecurrent prostate cancer: Added value of apparent diffusion coefficient maps and dynamic contrast-enhanced images	Study population have high risk prostate cancer
Abdi (2015)	Multiparametric magnetic resonance imaging enhances detection of significant tumor in patients on active surveillance for prostate cancer	Reference standard in study does not match that specified in protocol
Abdollah (2011)	Trans-rectal versus trans-perineal saturation rebiopsy of the prostate: Is there a difference in cancer detection rate?	Reference standard in study does not match that specified in protocol
Abedi (2017)	Multiparametric magnetic resonance imaging of prostate cancer: Association of quantitative magnetic resonance parameters with histopathologic findings	Reference standard in study does not match that specified in protocol
Abouassaly (2008)	Staging Saturation Biopsy in Patients with Prostate Cancer on Active Surveillance Protocol	Study does not contain any relevant index tests
Abu (2011)	The use of MRI scanning to triage patients	Review article but not a systematic review
Acar (2015)	Multiparametric MRI guidance in first-time prostate biopsies: What is the real benefit?	Reference standard in study does not match that specified in protocol

Short Title	Title	Reason for exclusion
An (2018)	Ruling out clinically significant prostate cancer with negative multi-parametric MRI	Reference standard in study does not match that specified in protocol
Anastasiadis (2015)	What Burden of Prostate Cancer Can Radiologists Rule Out on Multiparametric Magnetic Resonance Imaging? A Sensitivity Analysis Based on Varying the Target Condition in Template Prostate Mapping Biopsies	Not possible to calculate a 2x2 table from data presented in the study
Arumainaya gam (2010)	Accuracy of multiparametric magnetic resonance imaging in detecting recurrent prostate cancer after radiotherapy	Does not contain a population of people with suspected/low risk/intermediate prostate cancer
Barrett (2016)	Targeted transperineal biopsy of the prostate has limited additional benefit over background cores for larger MRI-identified tumors	Reference standard in study does not match that specified in protocol
Barrett (2017)	The emerging role of MRI in prostate cancer active surveillance and ongoing challenges	Review article but not a systematic review
Barzell (2007)	Appropriate Patient Selection in the Focal Treatment of Prostate Cancer: The Role of Transperineal 3-Dimensional Pathologic Mapping of the Prostate-A 4-Year Experience	Study does not contain any relevant index tests
Becker (2017)	Direct comparison of PI-RADS version 2 and version 1 regarding interreader agreement and diagnostic accuracy for the detection of clinically significant prostate cancer	Reference standard in study does not match that specified in protocol
Bittner (2013)	Incidence and pathological features of prostate cancer detected on transperineal template guided mapping biopsy after negative transrectal ultrasound guided biopsy	Only included population with negative TRUS/MRI results
Bjurlin (2016)	Multiparametric MRI and targeted prostate biopsy: Improvements in cancer detection, localization, and risk assessment	Reference standard in study does not match that specified in protocol
Bladou (2017)	Transrectal ultrasound-guided biopsy for prostate cancer detection: Systematic and/or magnetic-resonance imaging-targeted	Reference standard in study does not match that specified in protocol
Boesen (2015)	Early experience with multiparametric magnetic resonance imaging-targeted biopsies under visual transrectal ultrasound guidance in patients suspicious for prostate cancer undergoing repeated biopsy	Reference standard in study does not match that specified in protocol

Short Title	Title	Reason for exclusion
Borkowetz (2015)	Assessment of tumour aggressiveness in tranperineal mri/ultrasound-fusion biopsy in comparison to transrectal systematic prostate biopsy	Conference abstract
Borkowetz (2015)	Comparison of systematic transrectal biopsy to transperineal magnetic resonance imaging/ultrasound-fusion biopsy for the diagnosis of prostate cancer	Reference standard in study does not match that specified in protocol
Bosco (2016)	Confirmatory biopsy for the assessment of prostate cancer in men considering active surveillance: Reference centre experience	Not possible to calculate a 2x2 table from data presented in the study
Brock (2015)	Detecting Prostate Cancer	Not a relevant study design (crosssectional study) The study was of a case/control design
Brown (2015)	PROMIS - Prostate MR imaging study: A paired validating cohort study evaluating the role of multi-parametric MRI in men with clinical suspicion of prostate cancer	Duplicate reference
Castellucci (2015)	Magnetic resonance spectroscopic imaging 3T and prostate cancer: correlation with transperineal ultrasound guided prostate biopsy	Reference standard in study does not match that specified in protocol TRUS biopsy
Chen (2015)	3-tesla magnetic resonance imaging improves the prostate cancer detection rate in transrectral ultrasound-guided biopsy	Reference standard in study does not match that specified in protocol Systematic biopsy/TRUS biopsy
Chen (2017)	Outcomes of combination MRI-targeted and transperineal template biopsy in restaging low-risk prostate cancer for active surveillance	Men with no suspicious lesions were excluded from the study and reference standard was robotic transperineal template biopsy
Cool (2016)	Comparison of prostate MRI-3D transrectal ultrasound fusion biopsy for first-time and repeat biopsy patients with previous atypical small acinar proliferation	Reference standard in study does not match that specified in protocol
Di Franco (2017)	A retrospective comparison between transrectal and transperineal prostate biopsy in the detection of prostate cancer	Not a relevant study design (cross-sectional study) and Full text screening (diagnostic) and Reference standard in study does not match that specified in protocol
Dieffenbacher (2017)	Diagnostic accuracy of transperineal MRI fusion biopsy in comparison to transrectal biopsy with regard to	Reference standard in study does not match that specified in protocol

Short Title	Title	Reason for exclusion
	incidental histopathological findings in transurethral resection of the prostate	
Dikaios (2014)	Logistic regression model for diagnosis of transition zone prostate cancer on multi-parametric MRI	Not possible to calculate a 2x2 table from data presented in the study
Dikaios (2015)	Zone-specific logistic regression models improve classification of prostate cancer on multi-parametric MRI	Duplicate reference
Donaldson (2017)	The smarttarget biopsy trial: a prospective paired blinded trial with randomisation to compare visual-estimation and image-fusion targeted prostate biopsies	Conference abstract
Durand (2017)	Magnetic resonance microscopy may enable distinction between normal histomorphological features and prostate cancer in the resected prostate gland	Reference standard in study does not match that specified in protocol
Elkhoury (2017)	Targeted Prostate Biopsy in the Era of Active Surveillance	Review article but not a systematic review
Elkjaer (2017)	Multi-parametric magnetic resonance imaging and magnetic resonance guided biopsies at active surveillance inclusion selects prostate cancer patients for active treatment	Duplicate reference
El-Shater (2015)	PROMIS--Prostate MR imaging study: A paired validating cohort study evaluating the role of multi-parametric MRI in men with clinical suspicion of prostate cancer	Protocol article
Faiella (2018)	Analysis of histological findings obtained combining US/mp-MRI fusion-guided biopsies with systematic US biopsies: mp-MRI role in prostate cancer detection and false negative	Reference standard in study does not match that specified in protocol
Felker (2016)	In-bore magnetic resonance-guided transrectal biopsy for the detection of clinically significant prostate cancer	Reference standard in study does not match that specified in protocol
Ferriero (2016)	Diagnostic performance of multiparametric MRI in prostate cancer: per core analysis of two prospective ultrasound/MRI fusion biopsy datasets	Conference abstract
Fusco (2017)	A systematic review on multiparametric MR imaging in prostate cancer detection	Systematic review- not clear what the reference standard was for this systematic review
Futterer (2015)	Can Clinically Significant Prostate Cancer Be Detected with Multiparametric Magnetic Resonance	All relevant studies were included in the review

Short Title	Title	Reason for exclusion
	Imaging? A Systematic Review of the Literature	
Garcia (2016)	Transperineal versus transrectal prostate biopsy in prostate cancer detection: a systematic review with meta-analysis	Conference abstract
Garcia (2016)	Does transperineal prostate biopsy reduce complications compared with transrectal biopsy? A systematic review and metaanalysis of randomised controlled trials	Conference abstract
Garcia (2017)	Evaluation of MR imaging-targeted biopsies of the prostate in biopsy-naive patients. A single centre study	Reference standard in study does not match that specified in protocol Systematic Biopsy/Trus guided transperineal biopsy
Gayet (2016)	The value of magnetic resonance imaging and ultrasonography (MRI/US)-fusion biopsy platforms in prostate cancer detection: A systematic review	Reference standard in study does not match that specified in protocol (Systematic review)
Gaziev (2016)	Defining the learning curve for multiparametric magnetic resonance imaging (MRI) of the prostate using MRI-transrectal ultrasonography (TRUS) fusion-guided transperineal prostate biopsies as a validation tool	Investigating user technique
Gnanapragasam (2016)	The Prostate Health Index adds predictive value to multi-parametric MRI in detecting significant prostate cancers in a repeat biopsy population	Reference standard in study does not match that specified in protocol
Gomez-Iturriaga (2017)	Transperineal biopsies of MRI-detected aggressive index lesions in low- and intermediate-risk prostate cancer patients: Implications for treatment decision	Not possible to calculate a 2x2 table from data presented in the study
Gordetsky (2016)	Perineural Invasion in Prostate Cancer Is More Frequently Detected by Multiparametric MRI Targeted Biopsy Compared With Standard Biopsy	Reference standard in study does not match that specified in protocol
Grey (2015)	Diagnostic accuracy of magnetic resonance imaging (MRI) prostate imaging reporting and data system (PI-RADS) scoring in a transperineal prostate biopsy setting	Not possible to calculate a 2x2 table from data presented in the study
Grummet (2017)	How to Biopsy: Transperineal Versus Transrectal, Saturation Versus Targeted, What's the Evidence?	Review article but not a systematic review
Habchi (2014)	Value of prostate multiparametric magnetic resonance imaging for	No reference standard

Short Title	Title	Reason for exclusion
	predicting biopsy results in first or repeat biopsy	
Habibian (2017)	Imaging Characteristics of Prostate Cancer Patients Who Discontinued Active Surveillance on 3-T Multiparametric Prostate MRI	Reference standard in study does not match that specified in protocol
Hakozaki (2017)	A prospective study of magnetic resonance imaging and ultrasonography (MRI/US)-fusion targeted biopsy and concurrent systematic transperineal biopsy with the average of 18-cores to detect clinically significant prostate cancer	Reference standard in study does not match that specified in protocol Combined reference standard
Hamoen (2018)	Value of Serial Multiparametric Magnetic Resonance Imaging and Magnetic Resonance Imaging-guided Biopsies in Men with Low-risk Prostate Cancer on Active Surveillance After 1 Yr Follow-up	Reference standard in study does not match that specified in protocol
Hansen (2016)	Magnetic Resonance and Ultrasound Image Fusion Supported Transperineal Prostate Biopsy Using the Ginsburg Protocol: Technique, Learning Points, and Biopsy Results	Combined reference standard
Hansen (2016)	Multiparametric Prostate Magnetic Resonance Imaging and Cognitively Targeted Transperineal Biopsy in Patients With Previous Abdominoperineal Resection and Suspicion of Prostate Cancer	No reference standard
Hansen (2017)	Sub-differentiating equivocal PI-RADS-3 lesions in multiparametric magnetic resonance imaging of the prostate to improve cancer detection	No reference standard
Hansford (2014)	Dynamic contrast-enhanced MR imaging features of the normal central zone of the prostate	Reference standard in study does not match that specified in protocol
Hausmann (2018)	Prostate cancer detection among readers with different degree of experience using ultra-high b-value diffusion-weighted Imaging: Is a non-contrast protocol sufficient to detect significant cancer?	Reference standard in study does not match that specified in protocol
Hauth (2015)	Multiparametric MRI of the prostate with three functional techniques in patients with PSA elevation before initial TRUS-guided biopsy	Reference standard in study does not match that specified in protocol
Hu (2012)	A biopsy simulation study to assess the accuracy of several transrectal ultrasonography (TRUS)-biopsy	Reference standard in study does not match that specified in protocol

Short Title	Title	Reason for exclusion
	strategies compared with template prostate mapping biopsies in patients who have undergone radical prostatectomy	
Ishioka (2017)	Computer-aided diagnosis of prostate cancer using a deep neural networks algorithm in prebiopsy multiparametric magnetic resonance imaging	Conference abstract
Jambor (2015)	Prebiopsy multiparametric 3T prostate MRI in patients with elevated PSA, normal digital rectal examination, and no previous biopsy	Reference standard in study does not match that specified in protocol
Jiang (2016)	Magnetic resonance imaging - Ultrasound fusion targeted biopsy outperforms standard approaches in detecting prostate cancer: A meta-analysis	Reference standard in study does not match that specified in protocol
Jones (2016)	Optimizing safety and accuracy of prostate biopsy	Review article but not a systematic review
Jue (2017)	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	Conference abstract
Kamoi (2008)	The Utility of Transrectal Real-Time Elastography in the Diagnosis of Prostate Cancer	Study does not contain any relevant index tests
Kanoun (2017)	18F-Choline Positron Emission Tomography/Computed Tomography and Multiparametric Magnetic Resonance Imaging for the Detection of Early Local Recurrence of Prostate Cancer Initially Treated by Radiation Therapy: comparison With Systematic 3-Dimensional Transperineal Mapping Biopsy	Study population have high risk prostate cancer
Kanthabalan (2014)	Biopsy strategies for selecting patients for focal therapy for prostate cancer	Review article but not a systematic review
Kanthabalan (2016)	Transperineal Magnetic Resonance Imaging-targeted Biopsy versus Transperineal Template Prostate Mapping Biopsy in the Detection of Localised Radio-recurrent Prostate Cancer	Men with no suspicious lesions were excluded from the study
Kapoor (2017)	Re: Diagnostic Accuracy of Multi-parametric MRI and TRUS Biopsy in Prostate Cancer (PROMIS): A Paired Validating Confirmatory Study	Review article but not a systematic review

Short Title	Title	Reason for exclusion
Kasivisvanathan (2013)	Transperineal magnetic resonance image targeted prostate biopsy versus transperineal template prostate biopsy in the detection of clinically significant prostate cancer	Included a mixed population of suspected prostate cancer and proven prostate cancer with no sub group analysis
Kravchick (2015)	Patients with Persistently Elevated PSA and Negative Results of TRUS-Biopsy: Does 6-Month Treatment with Dutasteride can Indicate Candidates for Re-Biopsy. What is the Best of Saturation Schemes: Transrectal or Transperineal Approach?	Reference standard in study does not match that specified in protocol
Kroenig (2016)	Diagnostic Accuracy of Robot-Guided, Software Based Transperineal MRI/TRUS Fusion Biopsy of the Prostate in a High Risk Population of Previously Biopsy Negative Men	Reference standard in study does not match that specified in protocol
Lai (2017)	Co-registration of MRI and ultrasound: Accuracy of targeting based on radiology-pathology correlation	Review article but not a systematic review
Lane (2008)	Saturation Technique Does Not Decrease Cancer Detection During Followup After Initial Prostate Biopsy	Study does not contain any relevant index tests
Le (2014)	Targeted prostate biopsy: Value of multiparametric magnetic resonance imaging in detection of localized cancer	Review article but not a systematic review
Lebovici (2015)	Value of Endorectal MRI in Romanian Men for High Risk of Prostate Cancer: MRI Findings Compared with Saturation Biopsy	Study population have high risk prostate cancer
Lee (2016)	Visually estimated MRI targeted prostate biopsy could improve the detection of significant prostate cancer in patients with a PSA level <10 ng/mL	Reference standard in study does not match that specified in protocol
Lee (2017)	Comparison of multiparametric and biparametric MRI in first round cognitive targeted prostate biopsy in patients with PSA levels under 10 ng/mL	Reference standard in study does not match that specified in protocol
Li (2014)	Transrectal saturation technique may improve cancer detection as an initial prostate biopsy strategy in men with prostate-specific antigen <10 ng/ml	Study does not contain any relevant index tests
Linder (2013)	Standard and saturation transrectal prostate biopsy techniques are equally accurate among prostate cancer active surveillance candidates	Reference standard in study does not match that specified in protocol
Lu (2017)	Negative Multiparametric Magnetic Resonance Imaging of the Prostate Predicts Absence of Clinically	Does not contain a population of people with suspected/low risk/intermediate prostate cancer

Short Title	Title	Reason for exclusion
	Significant Prostate Cancer on 12-Core Template Prostate Biopsy	
Ma (2017)	The Role of Multiparametric Magnetic Resonance Imaging/Ultrasound Fusion Biopsy in Active Surveillance	Reference standard in study does not match that specified in protocol
Mabjeesh (2012)	High detection rate of significant prostate tumours in anterior zones using transperineal ultrasound-guided template saturation biopsy	Study does not contain any relevant index tests
Mariotti (2018)	Incremental diagnostic value of targeted biopsy using MP-MRI-TRUS fusion versus 14-fragments prostatic biopsy: a prospective controlled study	Reference standard in study does not match that specified in protocol
Marra (2017)	Pathological concordance between prostate biopsies and radical prostatectomy using transperineal sector mapping biopsies: Validation and comparison with transrectal biopsies	Reference standard in study does not match that specified in protocol
Martorana (2017)	Lesion volume predicts prostate cancer risk and aggressiveness: validation of its value alone and matched with prostate imaging reporting and data system score	Conference abstract
McCammack (2016)	Restriction spectrum imaging improves MRI-based prostate cancer detection	Reference standard in study does not match that specified in protocol
Merrick (2017)	Transperineal template-guided mapping biopsy identifies pathologic differences between very-low-risk and low-risk prostate cancer: Implications for active surveillance	Study does not contain any relevant index tests
Merrick (2017)	Incidence, grade and distribution of prostate cancer following transperineal template-guided mapping biopsy in patients with atypical small acinar proliferation	Study does not contain any relevant index tests
Miakhil (2017)	Predictive value of multiparameteric MRI (MP-MRI) for the detection of prostate cancer using 12-core trus-guided prostate biopsy-a United Kingdom multicenter study	Conference abstract
Miano (2014)	Transperineal versus transrectal prostate biopsy for predicting the final laterality of prostate cancer: Are they reliable enough to select patients for focal therapy? Results from a multicenter international study	No reference standard
Moldovan (2017)	What Is the Negative Predictive Value of Multiparametric Magnetic Resonance Imaging in Excluding Prostate Cancer	All relevant studies were included in the review

Short Title	Title	Reason for exclusion
	at Biopsy? A Systematic Review and Meta-analysis from the European Association of Urology Prostate Cancer Guidelines Panel	
Moore (2013)	Image-guided prostate biopsy using magnetic resonance imaging-derived targets: A systematic review	Reference standard in study does not match that specified in protocol
Mukherjee (2014)	Magnetic resonance imaging-directed transperineal limited-mapping prostatic biopsies to diagnose prostate cancer: A scottish experience	Reference standard in study does not match that specified in protocol
Muthigi (2017)	Missing the Mark: prostate Cancer Upgrading by Systematic Biopsy over Magnetic Resonance Imaging/Transrectal Ultrasound Fusion Biopsy	Reference standard in study does not match that specified in protocol
Nakai (2017)	Transperineal template-guided saturation biopsy aimed at sampling one core for each milliliter of prostate volume: 103 cases requiring repeat prostate biopsy	Study does not contain any relevant index tests
Numao (2007)	Improved Accuracy in Predicting the Presence of Gleason Pattern 4/5 Prostate Cancer by Three-Dimensional 26-Core Systematic Biopsy	Reference standard in study does not match that specified in protocol
Oberlin (2016)	Diagnostic Value of Guided Biopsies: Fusion and Cognitive-registration Magnetic Resonance Imaging Versus Conventional Ultrasound Biopsy of the Prostate	Reference standard in study does not match that specified in protocol
Ong (2015)	Transperineal biopsy prostate cancer detection in first biopsy and repeat biopsy after negative transrectal ultrasound-guided biopsy: The Victorian Transperineal Biopsy Collaboration experience	No reference standard
Orczyk (2017)	Should we aim for the centre of an MRI prostate lesion? Correlation between MP-MRI and 3-dimensional 5mm transperineal prostate mapping biopsies from the promis trial	Conference abstract
Pal (2012)	The role of a standardized 36 core template-assisted transperineal prostate biopsy technique in patients with previously negative transrectal ultrasonography-guided prostate biopsies	Reference standard in study does not match that specified in protocol
Pepe (2011)	Does an inflammatory pattern at primary biopsy suggest a lower risk for	Study does not contain any relevant index tests

Short Title	Title	Reason for exclusion
	prostate cancer at repeated saturation prostate biopsy?	
Pepe (2015)	Anterior prostate biopsy at initial and repeat evaluation: is it useful to detect significant prostate cancer?	Reference standard in study does not match that specified in protocol
Pepe (2015)	Can 3-tesla pelvic phased-array multiparametric MRI avoid unnecessary repeat prostate biopsy in patients with PSA < 10 ng/mL?	Conference abstract
Pepe (2016)	Can MRI/TRUS fusion targeted biopsy replace saturation prostate biopsy in the re-evaluation of men in active surveillance?	Reference standard in study does not match that specified in protocol Saturation biopsy
Pepe (2016)	Detection rate for significant cancer at confirmatory biopsy in men enrolled in Active Surveillance protocol: 20 cores vs 30 cores vs MRI/TRUS fusion prostate biopsy	Reference standard in study does not match that specified in protocol Saturation Biopsy also known TRUS
Pepe (2017)	Confirmatory biopsy of men under active surveillance: extended versus saturation versus multiparametric magnetic resonance imaging/transrectal ultrasound fusion prostate biopsy	Reference standard in study does not match that specified in protocol extended and saturation biopsy both are TRUS biopsy
Pepe (2017)	Multiparametric MRI/TRUS fusion prostate biopsy: Advantages of a transperineal approach	Men with no suspicious lesions were excluded from the study
Pepe (2017)	Transperineal Versus Transrectal MRI/TRUS Fusion Targeted Biopsy: Detection Rate of Clinically Significant Prostate Cancer	Not possible to calculate a 2x2 table from data presented in the study
Pessoa (2017)	Value of 3-Tesla multiparametric magnetic resonance imaging and targeted biopsy for improved risk stratification in patients considered for active surveillance	Reference standard in study does not match that specified in protocol TRUS biopsy
Pokharel (2014)	Multi-parametric MRI findings of transitional zone prostate cancers: correlation with 3-dimensional transperineal mapping biopsy	Included a mixed population of suspected prostate cancer and proven prostate cancer with no sub group analysis
Raber (2012)	Does the transrectal ultrasound probe influence prostate cancer detection in patients undergoing an extended prostate biopsy scheme? Results of a large retrospective study	Reference standard in study does not match that specified in protocol
Radtke (2015)	Comparative Analysis of Transperineal Template Saturation Prostate Biopsy Versus Magnetic Resonance Imaging Targeted Biopsy with Magnetic	Only included population with negative TRUS/MRI results The reference standard was carried out in patients who had lesions classed as

Short Title	Title	Reason for exclusion
	Resonance Imaging-Ultrasound Fusion Guidance	PIRADS 2-5
Radtke (2015)	Comparative analysis of transperineal template saturation prostate biopsy versus magnetic resonance imaging targeted biopsy with magnetic resonance imaging-ultrasound fusion guidance	Duplicate reference
Reis (2015)	Gleason underestimation is predicted by prostate biopsy core length	Reference standard in study does not match that specified in protocol
Robertson (2014)	Prostate cancer risk inflation as a consequence of image-targeted biopsy of the prostate: A computer simulation study	Reference standard in study does not match that specified in protocol
Russo (2015)	Detection of prostate cancer index lesions with multiparametric magnetic resonance imaging (mp-MRI) using whole-mount histological sections as the reference standard	Reference standard in study does not match that specified in protocol
Salami (2014)	Multiparametric magnetic resonance imaging outperforms the prostate cancer prevention trial risk calculator in predicting clinically significant prostate cancer	Reference standard in study does not match that specified in protocol
Scheltema (2017)	Preliminary Diagnostic Accuracy of Multiparametric Magnetic Resonance Imaging to Detect Residual Prostate Cancer Following Focal Therapy with Irreversible Electroporation	Does not contain a population of people with suspected/low risk/intermediate prostate cancer
Schimmoller (2016)	Targeted MRI-guided prostate biopsy: are two biopsy cores per MRI-lesion required?	Reference standard in study does not match that specified in protocol
Schimmoller (2016)	MRI-guided in-bore biopsy: Differences between prostate cancer detection and localization in primary and secondary biopsy settings	Reference standard in study does not match that specified in protocol
Schoots (2015)	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	Reference standard in study does not match that specified in protocol
Scott (2015)	Is transperineal prostate biopsy more accurate than transrectal biopsy in determining final Gleason score and clinical risk category? A comparative analysis	Not a relevant study design (cross sectional study)

Short Title	Title	Reason for exclusion
Sheikh (2017)	Combined T2 and diffusion-weighted MR imaging with template prostate biopsies in men suspected with prostate cancer but negative transrectal ultrasound-guided biopsies	Reference standard in study does not match that specified in protocol
Shen (2012)	The results of transperineal versus transrectal prostate biopsy: A systematic review and meta-analysis	Not a relevant study design (cross sectional study)
Shin (2018)	Diagnostic accuracy of a five-point Likert scoring system for magnetic resonance imaging (MRI) evaluated according to results of MRI/ultrasonography image-fusion targeted biopsy of the prostate	Reference standard in study does not match that specified in protocol
Shoji (2015)	Manually controlled targeted prostate biopsy with real-time fusion imaging of multiparametric magnetic resonance imaging and transrectal ultrasound: An early experience	Reference standard in study does not match that specified in protocol
Shoji (2017)	Accuracy of real-time magnetic resonance imaging-transrectal ultrasound fusion image-guided transperineal target biopsy with needle tracking with a mechanical position-encoded stepper in detecting significant prostate cancer in biopsy-naive men	Reference standard in study does not match that specified in protocol
Shukla-Dave (2014)	Role of MRI in prostate cancer detection	Review article but not a systematic review
Sim (2017)	Evaluation of tumor morphologies at radical prostatectomy in high risk gleason score >9 prostate cancer diagnosed at trus-guided biopsy	Conference abstract
Taira (2013)	Transperineal template-guided mapping biopsy as a staging procedure to select patients best suited for active surveillance	Study does not contain any relevant index tests
Takuma (2012)	Transperineal ultrasound-guided multiple core biopsy using template for patients with one or more previous negative biopsies: comparison with systematic 10-core biopsy	Conference abstract
Taneja (2017)	Re: Diagnostic Accuracy of Multi-Parametric MRI and TRUS Biopsy in Prostate Cancer (PROMIS): A Paired Validating Confirmatory Study	Review article but not a systematic review
Tay (2017)	Focal Therapy for Prostate Cancer with In-Bore MR-guided Focused Ultrasound: Two-Year Follow-up of a	No reference standard

Short Title	Title	Reason for exclusion
	Phase I Trial-Complications and Functional Outcomes	
Taymoorian (2007)	Transrectal broadband-Doppler sonography with intravenous contrast medium administration for prostate imaging and biopsy in men with an elevated PSA value and previous negative biopsies	Study does not contain any relevant index tests
Tewes (2017)	Evaluation of MRI/Ultrasound Fusion-Guided Prostate Biopsy Using Transrectal and Transperineal Approaches	Reference standard in study does not match that specified in protocol
Thestrup (2016)	Biparametric versus multiparametric MRI in the diagnosis of prostate cancer	Reference standard in study does not match that specified in protocol
Thompson (2014)	Multiparametric magnetic resonance imaging guided diagnostic biopsy detects significant prostate cancer and could reduce unnecessary biopsies and over detection: A prospective study	Reference standard in study does not match that specified in protocol
Thompson (2015)	Prospective study of pre-biopsy multiparametric magnetic resonance imaging (MP-MRI) compared to transperineal template mapping biopsy (TTMB) for detection of clinically significant prostate cancer: is it accurate enough to guide selection of men for biopsy?	Conference abstract
Thompson (2015)	Medium-term oncological outcomes for extended vs saturation biopsy and transrectal vs transperineal biopsy in active surveillance for prostate cancer	Not possible to calculate a 2x2 table from data presented in the study
Thompson (2016)	The diagnostic performance of multiparametric magnetic resonance imaging to detect significant prostate cancer	only included population with negative TRUS/MRI results Biopsy only carried out in those with MP-MRI SCORES OF 3-5
Thompson (2017)	Diagnostic accuracy of multi-parametric MRI and transrectal ultrasound-guided biopsy in prostate cancer	Review article but not a systematic review
Ting (2016)	Assessment of the Performance of Magnetic Resonance Imaging/Ultrasound Fusion Guided Prostate Biopsy against a Combined Targeted Plus Systematic Biopsy Approach Using 24-Core Transperineal Template Saturation Mapping Prostate Biopsy	Not possible to calculate a 2x2 table from data presented in the study

Short Title	Title	Reason for exclusion
Toner (2015)	Magnetic resonance imaging for prostate cancer: Comparative studies including radical prostatectomy specimens and template transperineal biopsy	All relevant studies were included in the review
Tran (2017)	Magnetic Resonance Imaging-Ultrasound Fusion Biopsy During Prostate Cancer Active Surveillance	Reference standard in study does not match that specified in protocol
Valerio (2015)	Visually directed vs. software-based targeted biopsy compared to transperineal template mapping biopsy in the detection of clinically significant prostate cancer	Men with no suspicious lesions were excluded from the study
Van Vugt (2012)	Prospective validation of a risk calculator which calculates the probability of a positive prostate biopsy in a contemporary clinical cohort	Reference standard in study does not match that specified in protocol
Walton (2015)	Use of serial multiparametric magnetic resonance imaging in the management of patients with prostate cancer on active surveillance	Reference standard in study does not match that specified in protocol
Wang (2015)	Evaluation of multiparametric magnetic resonance imaging in detection and prediction of prostate cancer	Reference standard in study does not match that specified in protocol
Wang (2017)	Primary prostate cancer imaging with MP-MRI, PET/CT and PET/MRI with focus on localisation and grading	Conference abstract
Weaver (2016)	Presence of magnetic resonance imaging suspicious lesion predicts gleason 7 or greater prostate cancer in biopsy-naive patients	Not possible to calculate a 2x2 table from data presented in the study
Wegelin (2016)	An Ex Vivo Phantom Validation Study of an MRI-Transrectal Ultrasound Fusion Device for Targeted Prostate Biopsy	Does not contain a population of people with suspected/low risk/intermediate prostate cancer
Westhoff (2017)	Precision of MRI/ultrasound-fusion biopsy in prostate cancer diagnosis: an ex vivo comparison of alternative biopsy techniques on prostate phantoms	Does not contain a population of people with suspected/low risk/intermediate prostate cancer The study is ex vivo
Winter (2013)	A systematic review with metaanalysis of transrectal prostate biopsy versus transperineal prostate biopsy for detecting prostate cancer	Conference abstract
Wu (2017)	T2* mapping combined with conventional T2-weighted image for prostate cancer detection at 3.0T MRI: A multi-observer study	Reference standard in study does not match that specified in protocol

Short Title	Title	Reason for exclusion
Wysock (2014)	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	Reference standard in study does not match that specified in protocol
Yoo (2017)	Is suspicious upstaging on multiparametric magnetic resonance imaging useful in improving the reliability of Prostate Cancer Research International Active Surveillance (PRIAS) criteria? Use of the K-CaP registry	Reference standard in study does not match that specified in protocol
Zhang (2015)	Free-hand transperineal targeted prostate biopsy with real-time fusion imaging of multiparametric magnetic resonance imaging and transrectal ultrasound: single-center experience in China	Men with no suspicious lesions were excluded from the study Population was restricted to those with PIRAD classification between 2 and 5 according to the MP-MRI
Zhang (2017)	Comparison of free-hand transperineal MP-MRI/TRUS fusion-guided biopsy with transperineal 12-core systematic biopsy for the diagnosis of prostate cancer: a single-center prospective study in China	Reference standard in study does not match that specified in protocol TRUS biopsy

Randomised control studies

Short Title	Title	Reason for Exclusion
Arsov (2015)	Prospective randomized trial comparing magnetic resonance imaging (MRI)-guided in-bore biopsy to MRI-ultrasound fusion and transrectal ultrasound-guided prostate biopsy in patients with prior negative biopsies	Does not contain a population of people who are biopsy naive
Arsov (2015)	A prospective randomized study comparing MR-guided in-bore versus MRI/ultrasound fusion guided prostate biopsy in patients with prior tumor-negative TRUS biopsy	Conference abstract
Arsov (2016)	Comparison of patient comfort between MR-guided in-bore and MRI/ultrasound fusion-guided prostate biopsies within a prospective randomized trial	Study does not contain any relevant interventions
Baur (2017)	A prospective study investigating the impact of multiparametric MRI in biopsy-naive patients with clinically suspected prostate cancer: The PROKOMB study	Study does not contain any relevant interventions Not a randomised controlled trial
Cam (2008)	Combined periprostatic and intraprostatic local anesthesia for prostate biopsy: a double-blind, placebo controlled, randomized trial	Study does not contain any relevant interventions
Chae (2009)	The comparison between transperineal and transrectal ultrasound-guided prostate needle biopsy	Study not reported in English
Choi (2011)	Prospective evaluation of 3T magnetic resonance imaging performed prior to an initial transrectal ultrasound-guided biopsy in the detection of prostate cancer	Conference abstract
Cicione (2012)	Prostate biopsy quality is independent of needle size: a randomized single-center prospective study	Study does not contain any relevant interventions
Davuluri (2015)	The Comparison of Magnetic Resonance Image-Guided Targeted Biopsy Versus Standard Template Saturation Biopsy in the Detection of Prostate Cancer	Review article but not a systematic review
Dell'Oglio (2017)	Inclusion of mpMRI into the European Randomized study of Screening for Prostate Cancer (ERSPC) risk calculator: a new proposal to improve the accuracy of prostate cancer detection	Conference abstract

Short Title	Title	Reason for Exclusion
Diagnostic performance... (2016)	Diagnostic performance of power doppler and ultrasound contrast agents in early imaging-based diagnosis of organ-confined prostate cancer: is it possible to spare cores with contrast-guided biopsy?	Not a randomised controlled trial
DiBianco (2016)	Ultrasound Guided, Freehand Transperineal Prostate Biopsy: An Alternative to the Transrectal Approach	Not a randomised controlled trial
Fiard (2013)	Targeted MRI-guided prostate biopsies for the detection of prostate cancer: initial clinical experience with real-time 3-dimensional transrectal ultrasound guidance and magnetic resonance/transrectal ultrasound image fusion	Not a randomised controlled trial
Garcia (2016)	Transperineal versus transrectal prostate biopsy in prostate cancer detection: a systematic review with meta-analysis	Conference abstract
Garcia (2016)	Does transperineal prostate biopsy reduce complications compared with transrectal biopsy? A systematic review and metaanalysis of randomised controlled trials	Conference abstract
Gayet (2016)	The value of magnetic resonance imaging and ultrasonography (MRI/US)-fusion biopsy platforms in prostate cancer detection: a systematic review	Systematic review - looking at diagnostic test accuracy studies
Grenabo (2016)	Role of Magnetic Resonance Imaging in Prostate Cancer Screening: a Pilot Study Within the Göteborg Randomised Screening Trial	Does not contain a population of people who biopsy naive
Grummet (2017)	Transperineal vs. transrectal biopsy in MRI targeting	Review article but not a systematic review
Guo (2015)	Comparison between Ultrasound Guided Transperineal and Transrectal Prostate Biopsy: a Prospective, Randomized, and Controlled Trial	Duplicate reference
Guo (2015)	Comparison between Ultrasound Guided Transperineal and Transrectal Prostate Biopsy: A Prospective, Randomized, and Controlled Trial	Comparator in study does not match that specified in protocol both arms are systematic biopsy
Halpern (2012)	Contrast enhanced transrectal ultrasound for the detection of prostate cancer: a randomized, double-blind trial of dutasteride pretreatment	Study does not contain any relevant interventions

Short Title	Title	Reason for Exclusion
Hara (2008)	Optimal approach for prostate cancer detection as initial biopsy: prospective randomized study comparing transperineal versus transrectal systematic 12-core biopsy	Comparator in study does not match that specified in protocol Both arms are systematic biopsies
Kasivisvanathan (2015)	A randomized controlled trial to investigate magnetic resonance imaging-targeted biopsy as an alternative diagnostic strategy to transrectal ultrasound-guided prostate biopsy in the diagnosis of prostate cancer	Not a randomised controlled trial
Kasivisvanathan (2017)	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	Study Protocol
Klotz (2017)	Magnetic resonance imaging-targeted vs. systematic biopsies in men on active surveillance: results of a prospective, randomized Canadian Urology Research Consortium trial	Conference abstract
Leitao (2011)	A prospective randomized trial of prostate biopsy protocols comparing the vienna nomogram and a standard 10-core biopsy scheme	Conference abstract
Leitao (2017)	A Prospective Randomized Trial Comparing the Vienna Nomogram and a Ten-Core Prostate Biopsy Protocol: Effect on Cancer Detection Rate	Study does not contain any relevant interventions
Lenherr (2013)	Real-time-elastography (RTE): its detection rate compared to multiple core biopsy and an evaluation of psa and prostate volume as predictors	Conference abstract
Mitterberger (2007)	A prospective randomized trial comparing contrast-enhanced targeted versus systematic ultrasound guided biopsies: impact on prostate cancer detection	Study does not contain any relevant interventions
Panebianco (2010)	Role of magnetic resonance spectroscopic imaging ([1H]MRSI) and dynamic contrast-enhanced MRI (DCE-MRI) in identifying prostate cancer foci in patients with negative biopsy and high levels of prostate-specific antigen (PSA)	Study does not contain any relevant interventions
Panebianco (2015)	Multiparametric magnetic resonance imaging vs. standard care in men	Comparator in study does not match that

Short Title	Title	Reason for Exclusion
	being evaluated for prostate cancer: a randomized study	specified in protocol
Park (2011)	Prospective evaluation of 3-T MRI performed before initial transrectal ultrasound-guided prostate biopsy in patients with high prostate-specific antigen and no previous biopsy	Duplicate reference
Porpiglia (2017)	A prospective randomized study comparing standard prostate biopsy and a new diagnostic path with MRI and fusion biopsy: results after two years	Conference abstract
Porpiglia (2017)	Standard prostate biopsy Versus MRI-fusion biopsy: results after two years of a prospective randomized study	Conference abstract
Sciarra (2012)	Multiparametric magnetic resonance imaging of the prostate can improve the predictive value of the urinary prostate cancer antigen 3 test in patients with elevated prostate-specific antigen levels and a previous negative biopsy	Does not contain a population of people who are biopsy naive
Shah (2017)	Magnetic resonance imaging in the early detection of prostate cancer and review of the literature on magnetic resonance imaging-stratified clinical pathways	Review article but not a systematic review
Singh (2017)	Comparison of infective complications in transperineal versus transrectal ultrasound guided prostatic biopsy in patients suspected to have prostate cancer	Conference abstract
Takenaka (2008)	A prospective randomized comparison of diagnostic efficacy between transperineal and transrectal 12-core prostate biopsy	Comparator in study does not match that specified in protocol both arms are systematic biopsy
Takuma (2012)	Transperineal ultrasound-guided multiple core biopsy using template for patients with one or more previous negative biopsies: comparison with systematic 10-core biopsy	Conference abstract
Taverna (2016)	Endorectal multiparametric 3-tesla magnetic resonance imaging associated with systematic cognitive biopsies does not increase prostate cancer detection rate: a randomized prospective trial	Does not contain a population of people who are biopsy naive

Short Title	Title	Reason for Exclusion
Thompson (2015)	Prospective study of pre-biopsy multiparametric magnetic resonance imaging (MPMRI) compared to transperineal template mapping biopsy (TTMB) for detection of clinically significant prostate cancer: is it accurate enough to guide selection of men for biopsy?	Conference abstract
van Hove (2014)	Comparison of image-guided targeted biopsies versus systematic randomized biopsies in the detection of prostate cancer: a systematic literature review of well-designed studies	Systematic review - all relevant studies have been included in this review
Wegelin (2016)	An interim analysis of the FUTURE trial; A RCT on three techniques of target prostate biopsy based on MR imaging. Comparison of detection rates of (significant) prostate cancer	Conference abstract
Winter (2013)	A systematic review with metaanalysis of transrectal prostate biopsy versus transperineal prostate biopsy for detecting prostate cancer	Conference abstract

Economic studies

Short Title	Title	Reason for exclusion
Venderink et al. 2017	Cost-Effectiveness Comparison of Imaging-Guided Prostate Biopsy Techniques: Systematic Transrectal Ultrasound, Direct In-Bore MRI, and Image Fusion	Not using the trans-perineal mapping biopsy as a reference
Willis et al 2015	A review of economic evaluations of diagnostic strategies using imaging in men at risk of prostate cancer	Review reporting already identified studies
Pahwa et al 2017	Cost-effectiveness of MR Imaging-guided Strategies for Detection of Prostate Cancer in Biopsy-Naive Men	Not using the trans-perineal mapping biopsy as a reference
Loeb et al 2017	Active Surveillance Versus Watchful Waiting for Localized Prostate Cancer: A Model to Inform Decisions	Men diagnosed with localised PC. Not using the trans-perineal mapping biopsy as a reference
Gordon et al 2017	Cost-effectiveness analysis of multiparametric MRI with increased active surveillance for low-risk prostate cancer in Australia	Men diagnosed with localised PC. Not using the trans-perineal mapping biopsy as a reference
Do Rooij et al 2014	Cost-effectiveness of magnetic resonance (MR) imaging and MR-guided targeted biopsy versus	Not using the trans-perineal mapping biopsy as a reference

Short Title	Title	Reason for exclusion
	systematic transrectal ultrasound-guided biopsy in diagnosing prostate cancer: a modelling study from a health care perspective	
Cerantola et al 2016	Cost-effectiveness of multiparametric magnetic resonance imaging and targeted biopsy in diagnosing prostate cancer	Not using the trans-perineal mapping biopsy as a reference
Mowatt et al 2013	The diagnostic accuracy and cost-effectiveness of magnetic resonance spectroscopy and enhanced magnetic resonance imaging techniques in aiding the localisation of prostate abnormalities for biopsy: a systematic review and economic evaluation	Different population (patients with previous negative biopsy)
Hovels et al 2009	Cost-effectiveness of MR lymphography for the detection of lymph node metastases in patients with prostate cancer	population and comparator out of the scope (MR Lymphography for the Detection of Lymph Node Metastases in Patients with Prostate Cancer
Roth et al 2015	Cost-Effectiveness of a Biopsy-Based 8-Protein Prostate Cancer Prognostic Assay to Optimize Treatment Decision Making in Gleason 3 + 3 and 3 + 4 Early Stage Prostate Cancer	Comparators out of the scope (PCA3)
Nicholson et al 2015	The clinical effectiveness and cost-effectiveness of the PROGENSA prostate cancer antigen 3 assay and the Prostate Health Index in the diagnosis of prostate cancer: a systematic review and economic evaluation	Comparators out of the scope (PCA3)

Appendix I – References

Clinical studies - included - cross-sectional studies

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Clinical studies – excluded – cross-sectional studies

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Appendix J: Research Recommendations

Question	In patients with negative MRI (Likert score 1 or 2), what is the next best diagnostic investigation to rule out clinically significant prostate cancer?
Population	People with negative MRI (Likert score 1 or 2)
Index tests	Any test given within 6 months of MRI to further exclude clinically significant prostate cancer.
Reference standard	Biopsy
Outcomes	Sensitivity Specificity Positive and negative likelihood ratios QoL outcomes Adverse events
Study design	Diagnostic cross sectional studies
Potential criterion	**Explanation**
Importance to patients, service users or the population	The evidence shows that about 20% of men with a Likert score 1 or 2 on MRI may have clinically significant cancer. Since the new pathway discourages biopsy in men with negative MRI, the research will help formulate a pathway that these people may follow to identify any missed clinically significant cancer
Relevance to NICE guidance	Current guidance on the follow-up protocol for men with negative is not evidence based as this is a new population as a result as the new pathway.
Current evidence base	Limited evidence as this population is relatively new
Equality	No additional equality issues are envisaged relating to this study over and above those applying generally to vulnerable groups of people.
Feasibility	A large enough number of people receive a MRI of the prostate to make this study feasible.

Question	What is the diagnostic accuracy of transperineal mapping biopsy versus transperineal non mapping biopsy in the diagnosis of clinically significant prostate cancer?
Population	People suspected of cancer (biopsy naïve or repeat biopsy)
Index test	Transperineal non mapping biopsy
References	Transperineal mapping biopsy
Outcomes	Sensitivity Specificity Positive and Negative Likelihood ratios
Study design	Diagnostic cross sectional studies

Question	What is the diagnostic accuracy of transperineal mapping biopsy versus transperineal non mapping biopsy in the diagnosis of clinically significant prostate cancer?
Potential criterion	**Explanation**
Importance to patients, service users or the population	The committee explained that a number of providers across the country use the transperineal route for biopsy rather than the transrectal route, however transperineal biopsy can be a mapping biopsy where a large number of samples are taken from around the prostate (currently considered the 'gold standard' diagnostic test) or a non-mapping biopsy where a smaller number of samples are taken in a more focussed way (for example guided by MRI). The diagnostic accuracy of the non-mapping method is not known. Transperineal mapping biopsy is more resource intensive than non-mand the NHS is not equipped to perform a large number of these.
Relevance to NICE guidance	This research will enable NICE guideline to be more specific about which biopsy is most appropriate in which situation.
Current evidence base	The current evidence base suggests that transperineal template biopsy is the most accurate diagnostic tool for prostate cancer. It is unknown how non-mapping transperineal biopsy compares to this.
Equality	No additional equality issues are envisaged relating to this study over and above those applying generally to vulnerable groups of people.
Feasibility	There is a large enough population of people with locally advanced prostate cancer, carrying out a trial in this area should be feasible

Appendix K: PROMIS economic evaluation presentation

Cost-effectiveness of mpMRI, TRUS-biopsy and TPM-biopsy to diagnose clinically significant prostate cancer

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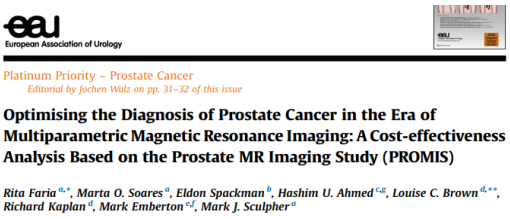
Marta O. Soares, Eldon Spackman, Hashim U. Ahmed, Louise C. Brown, Richard Kaplan, Mark Emberton and Mark J. Sculpher

Disclaimer

This presentation is based on the work conducted for the NIHR-HTA funded project 'Prostate MRI Imaging Study (PROMIS): Evaluation of Multi-Parametric Resonance Imaging in the Diagnosis and Characterisation of Prostate Cancer', published in European Urology and in a forthcoming HTA monograph.


European Association of Urology

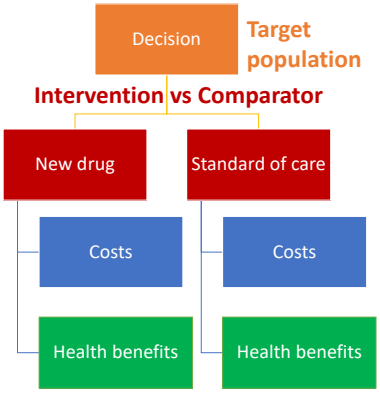
Platinum Priority – Prostate Cancer
Editorial by Jochen Walz on pp. 31–32 of this issue

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)

Rita Faria[a,], Marta O. Soares[a], Eldon Spackman[b], Hashim U. Ahmed[c,d], Louise C. Brown[d,**], Richard Kaplan[d], Mark Emberton[c,f], Mark J. Sculpher[a]*

Cost-effectiveness analysis

How to use CEA to inform decisions? (1)



Time horizon sufficiently long to reflect all important differences in costs or outcomes

Costs falling on the UK NHS

Quality-adjusted life years: Include life expectancy and health-related quality of life

How to use CEA to inform decisions? (2)

1. How the new drug compares with the standard of care?
   - Difference in costs;
   - Difference in health benefits (QALYs);
   - **Incremental cost-effectiveness ratio: ICER**.

2. How the cost-effectiveness of the new drug vs standard of care compared with everything else funded by the NHS?
   - **Cost-effectiveness threshold**: represents the productivity of the NHS in generating health.

How to use CEA to inform decisions? (3)

A cost-effectiveness threshold of £20,000-£30,000 per QALY means that the NHS loses 1 QALY if the additional costs of a new drug are £20,000.

→ A new drug is not cost-effective if it generates less than 1 QALY per £20,000-£30,000 expenditure.

→ This is equivalent to an ICER > £20,000-£30,000/QALY

Research suggests that the NHS threshold is £13,000/QALY.

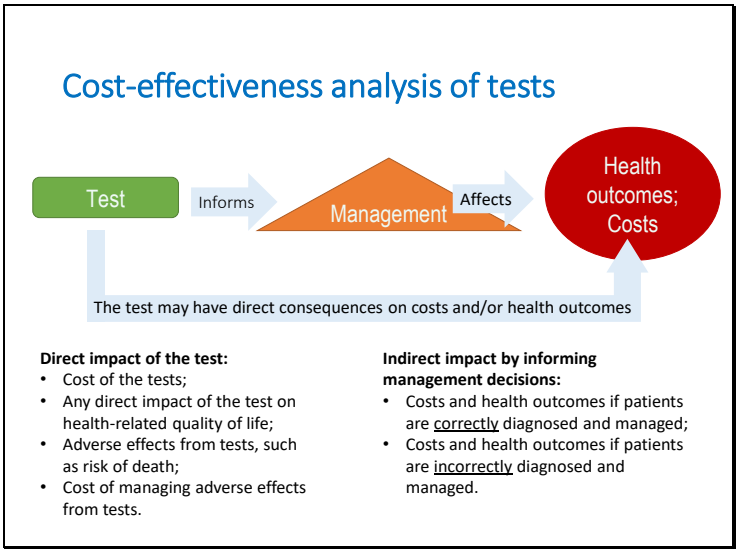
Carrying NICE over the threshold

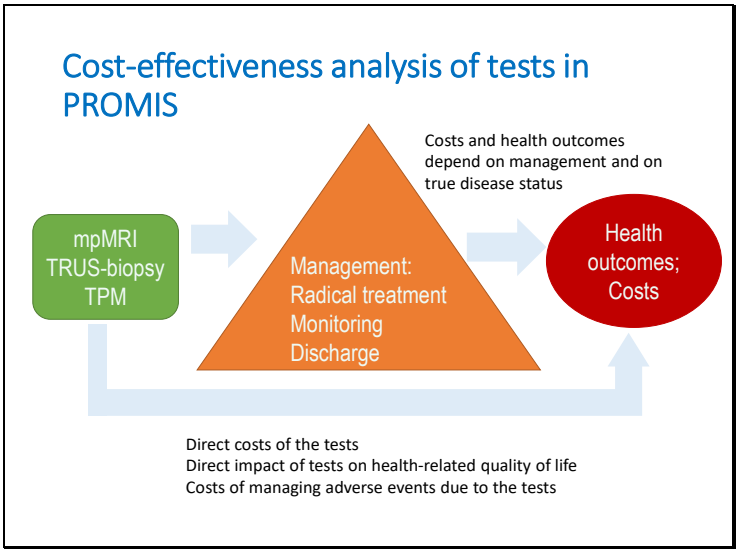
Share

Sir Andrew Dillon

Researchers at the University of York have argued that NICE is advising the NHS "to pay too much" for new drugs. NICE uses 'quality adjusted life years' (QALYs), to compare different drugs, devices and other technologies for different conditions. NICE's 'threshold,' over which treatments are less likely to be recommended for use in the NHS, is typically between £20,000 and £30,000 per QALY. New research led by Professor Karl Claxton suggests that paying more than £13,000 per QALY for technologies "does more harm than good" by displacing other more effective healthcare from the NHS. Sir Andrew Dillon, NICE's chief executive, says it's not as simple as that:

https://www.nice.org.uk/news/blog/carrying-nice-over-the-threshold


Cost-effectiveness analysis of tests
Test
Informs
Management
Affects
Health outcomes; Costs
The test may have direct consequences on costs and/or health outcomes
Direct impact of the test:
• Cost of the tests;
• Any direct impact of the test on health-related quality of life;
• Adverse effects from tests, such as risk of death;
• Cost of managing adverse effects from tests.
Indirect impact by informing management decisions:
• Costs and health outcomes if patients are correctly diagnosed and managed;
• Costs and health outcomes if patients are incorrectly diagnosed and managed.


Cost-effectiveness analysis of tests in PROMIS
Costs and health outcomes depend on management and on true disease status
mpMRI
TRUS-biopsy
TPM
Management:
Radical treatment
Monitoring
Discharge
Health outcomes; Costs
Direct costs of the tests
Direct impact of tests on health-related quality of life
Costs of managing adverse events due to the tests

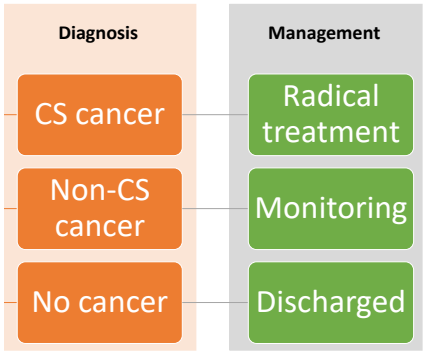
From diagnosis to management

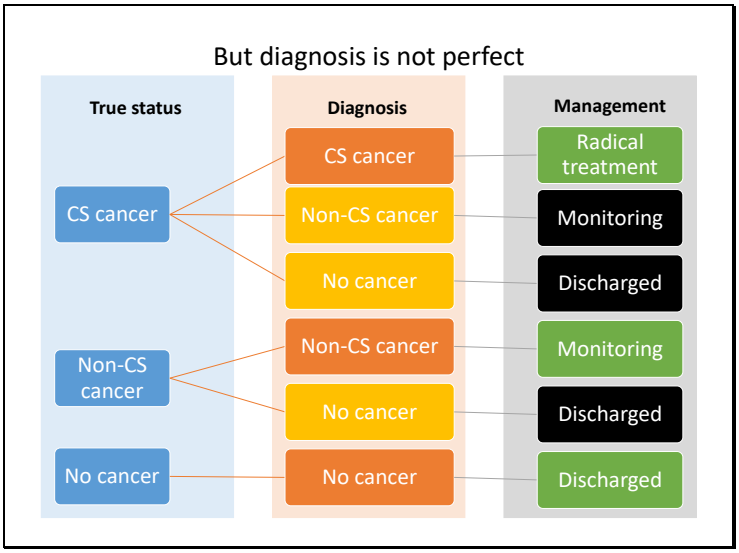
How does diagnosis informs management of prostate cancer?

Men with clinically significant prostate cancer should receive radical treatment.

Men with non-clinically significant prostate cancer can be monitored and receive treatment only if cancer progresses.

Men with no cancer can be discharged.



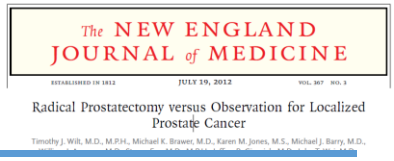


What is the evidence on long-term outcomes by management option?

- Objective: Find evidence on the long-term outcomes of men with CS cancer and non-CS cancer treated with radical treatment or monitoring.
- Approach: review of 2014 NICE guideline on prostate cancer; review of recent systematic reviews.
- 2 RCTs identified comparing radical prostatectomy vs watchful waiting.
  - PIVOT (Wilt et al) in the US.
  - SPCG-4 (Bill-Axelson et al) in Scandinavia.
- We chose PIVOT et al as source of long-term outcomes
  - PIVOT reports results by cancer risk subgroup: low risk, intermediate risk, and high risk.
  - → **need to map between the PIVOT and PROMIS classifications.**

The PIVOT trial

Country	US
Enrolment	1994-2002
Stage	T1-T2
Subgroups	Low risk, intermediate risk, high risk cancer
Trial arms	Observation N=367 Radical prostatectomy N=364
Outcomes	Overall survival, cancer survival, bone metastases
Follow-up	10 years



Wilt TJ, Brawer MK, Jones KM, et al. Radical prostatectomy versus observation for localized prostate cancer. N Engl J Med 2012;367:203-13. DOI: 10.1056/NEJMoa1113162

What is clinically significant (CS) prostate cancer in PROMIS?

Biopsy definitions

1. Dominant Gleason pattern ≥4 and/or any Gleason pattern ≥5 and/or cancer core length ≥6mm.
2. Any Gleason pattern ≥4 and/or cancer core length ≥4mm.

Imaging definitions

1. Lesion volume ≥0.5cc and/or Gleason score ≥4+3
2. Lesion volume ≥0.2cc and/or Gleason score ≥ 3+4.

Mapping between PIVOT and PROMIS

Group	Definition	PROMIS
No cancer	Men with no evidence of cancer at either TPMB or TRUSGB.	No cancer
Low risk cancer	Men with Gleason score ≤6 at either TRUSGB or TPMB, and PSA<10.	Non-CS cancer
Intermediate risk cancer	Men with Gleason score=7 either TRUSGB or TPMB, or PSA≥10.	CS cancer
High risk cancer	Men with Gleason score≥8 either TRUSGB or TPMB.	CS cancer

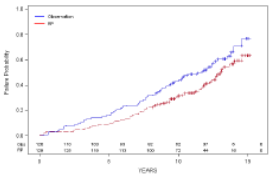
What information do we need?

		Diagnostic classification		
		No cancer	Non-CS cancer	CS cancer
True cancer status	No cancer	Discharge	-	-
	Low risk cancer	Discharge	Monitoring	-
	Intermediate risk cancer	Discharge	Monitoring	Radical treatment
	High risk cancer	Discharge	Monitoring	Radical treatment

Challenges in using PIVOT data for modelling

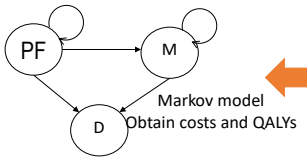
- The PIVOT trial compares radical prostatectomy with observation;
  - We assumed that observation in the PIVOT trial results in similar outcomes as monitoring as recommended by the 2014 NICE guideline
- The PIVOT trial stratified patients into cancer risk subgroups based on TRUS-biopsy, which is imperfect.
  - We assumed that the stratification is perfect.
- The follow-up of the PIVOT trial is incomplete.
  - We extrapolate to the long-term.
- The PIVOT trial reports cumulative incidence of metastasis, which does not allow for the direct estimation of transition probabilities from progression-free to metastasised cancer; and does not report the risk of death in men who progressed to metastasis.
  - We develop a calibration model to estimate transition probabilities using additional information.

From the PIVOT trial to costs and QALYs



Digitise survival curves
Obtain progression risk to metastatic cancer
Obtain mortality risk from metastatic cancer

Calibration model
Obtain transition probabilities



Markov model
Obtain costs and QALYs

Survival curve from Wilt TJ, Brawer MK, Jones KM, et al. Radical prostatectomy versus observation for localized prostate cancer. N Engl J Med 2012;367:203-13. DOI: 10.1056/NEJMoa1113162

Data to inform long-term model

Parameter	Source
Calibration to obtain transition probabilities	
Time to metastasis; time to death	PIVOT trial
Time from metastasis to death	STAMPEDE trial
Health-related quality of life	
Decrement from metastatic disease	Torvinen et al
Age-related decrement	Ara et al
Costs	
Watchful waiting per year	1 consultant appointment + 3 PSA tests
Radical prostatectomy (one off)	Cost of radical prostatectomy
Metastatic cancer	Cost of managing metastatic cancer Lord et al
Adverse events rates	PIVOT trial
Cost of adverse events	NHS PbR tariff and 2014 NICE guideline

Long-term health outcomes and costs

Subgroups	Management	Lifetime QALYs	Lifetime costs	ICER
Low	Monitoring	8.45 (7.99 to 8.94)	£3,994 (£3,301 to £4,894)	Not applicable
Intermediate	Monitoring	7.29 (6.65 to 8.03)	£4,130 (£3,215 to £5,351)	£3,067/QALY
	Radical treatment	8.23 (7.69 to 8.79)	£7,041 (£6,353 to £7,959)	
High	Monitoring	6.38 (5.59 to 7.36)	£3,764 (£2,804 to £5,001)	£3,602/QALY
	Radical treatment	7.21 (6.42 to 8.18)	£6,796 (£6,112 to £7,746)	

Additional cost per additional CS cancer detected

Which strategies offer the best yield in detecting CS cancer given the cost?

CS cancer	Cost
• True disease status	• Cost of the tests
• Diagnosis	• Cost of adverse events

Stages:

1. What are the strategies: how can mpMRI, TRUS-biopsy, and TPM-biopsy be used in combination to detect CS cancer?
2. What is the yield of each strategy?
3. What is the cost of each strategy?

How can the tests be used to diagnosed CS prostate cancer (1)?

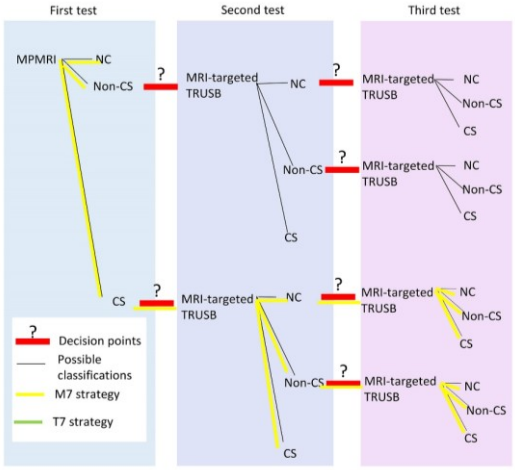
- 3 tests: TRUS-biopsy, mpMRI, TPM-biopsy.
- Constraints:
  - up to 3 tests;
  - Diagnosis requires confirmatory biopsy.

= 32 test sequences

How can the tests be used to diagnosed CS cancer (2)?

- **M**: strategies that start with mpMRI and use 1 or 2 TRUS-biopsies (M1 to M7).
- **N**: strategies that start with mpMRI and use at least 1 TPM-biopsy (N1 to N7).
- **T**: strategies that start with TRUS-biopsy and do not use TPM-biopsy (T1 to T9).
- **P**: strategies that start with TRUS-biopsy or TPM-biopsy, or use TPM-biopsy (P1 to P9).

Example diagnosis pathway with mpMRI as the first test



How can the tests be used to diagnosed CS cancer (3)?

- The tests can be used at different cut-offs:
  - **TRUS-biopsy:**
    - 2 definitions of CS prostate cancer.
      1. Dominant Gleason pattern ≥4 and/or any Gleason pattern ≥5 and/or cancer core length ≥6mm.
      2. Any Gleason pattern ≥4 and/or cancer core length ≥4mm.
  - **mpMRI:**
    - 2 definitions of CS cancer:
      1. Lesion volume ≥0.5cc and/or Gleason score ≥4+3
      2. Lesion volume ≥0.2cc and/or Gleason score ≥ 3+4.
    - 4 cut-offs in the scale: =5, ≥4, ≥3, ≥2, ≥1.

Examples (text)

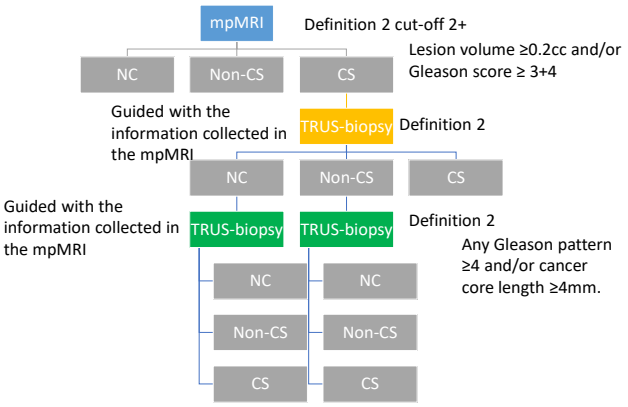
M7 222

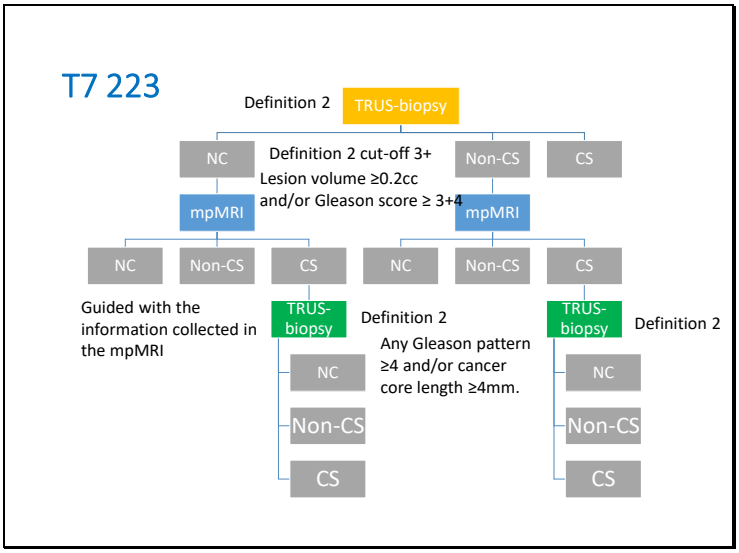
- **M7**: all men are assessed with mpMRI; men with suspicion of CS cancer receive a TRUS-biopsy. Men in whom CS cancer was not detected receive second TRUS-biopsy.
- **2**: TRUS-biopsy uses CS cancer definition 2 to diagnose CS cancer.
- **2**: mpMRI uses CS cancer definition 2 to indicate suspicion of CS cancer.
- **2**: lesions which score 2 and above are classified as CS cancer.

T7 223

- **T7**: all men receive a TRUS-biopsy; Men in whom CS cancer was not detected receive an mpMRI. Men with suspicion of CS cancer receive a second TRUS-biopsy.
- **2**: TRUS-biopsy uses CS cancer definition 2 to diagnose CS cancer.
- **2**: mpMRI uses CS cancer definition 2 to indicate suspicion of CS cancer.
- **3**: lesions which score 2 and above are classified as CS cancer.

M7 222

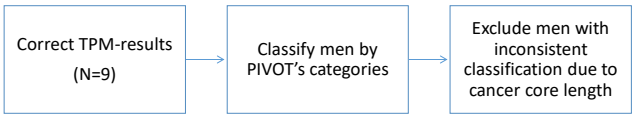




True disease status in PROMIS

Clinical study	Economic study
Categorises patients as having CS cancer or non-CS cancer (which includes no cancer).	Categorises patients as having high risk cancer, intermediate risk cancer, low risk cancer, and no cancer, so that long term outcomes can be mapped to the disease classification.
Uses TPM-biopsy as the reference standard.	Uses TPM-biopsy and TRUS-biopsy as reference standard, whichever is greatest. → Affects 9 men where TRUS-biopsy detected higher grade cancer than TPM-biopsy.
CS cancer definition includes cancer core length	The PIVOT trial definition does not include cancer core length. Including cancer core length assigned 7 men to a different risk category → these 7 men were excluded.

How was true disease status defined?



No cancer = 159 men
Low risk cancer = 91 men[(1)]
Intermediate risk cancer = 301 men
High risk cancer = 18 men

(1) 7 men with low risk cancer were excluded from the analysis because, according to the PIVOT risk categories, these men have low risk cancer, but according to the PROMIS CS cancer definition, these men have CS cancer due to their cancer core length.

Data on the sensitivity of TRUS-biopsy

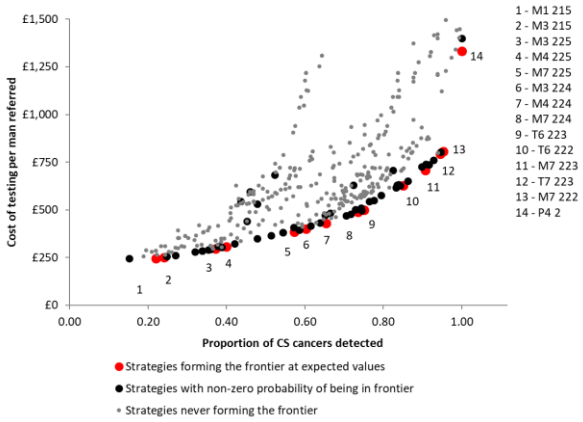
	Parameter	Source
1	First TRUS-biopsy without a prior mpMRI	PROMIS
2	Second TRUS-biopsy after a TRUS-biopsy which did not detect cancer	Roehl et al
3	Second TRUS-biopsy after a TRUS-biopsy which detected non-CS cancer	Barzell et al
4	First TRUS-biopsy after suspicious mpMRI	PROMIS combined with relative sensitivity from Schoots et al
5	Second TRUS-biopsy after suspicious mpMRI and the first TRUS-biopsy detecting no cancer	Schoots et al
6	Second TRUS-biopsy after suspicious mpMRI and after first biopsy detecting non-CS cancer	Assumed the same as (5)

Other parameters

Parameter	Source
Sensitivity and specificity of mpMRI	PROMIS
Adverse event	
From mpMRI	Assumed none
From TRUS-biopsy	Rosario et al
From TPM-biopsy	Pepe & Aragona
Costs	
Unit costs	NHS reference costs
Health-related quality of life impact from tests	
From mpMRI	Assumed zero based on PROMIS
From TRUS-biopsy	Assumed zero based on Essink-Bot et al
From TPM-biopsy	Decrement from combined biopsy procedure in PROMIS

Results

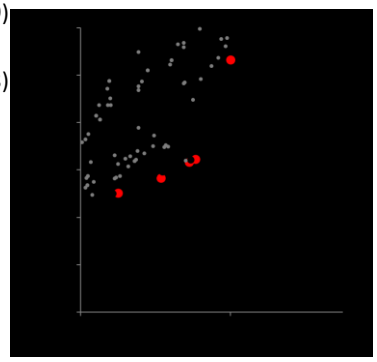
Additional cost per CS cancer detected



Which are the most sensitive strategies?

Proportion of CS cancer detected (95% CI)

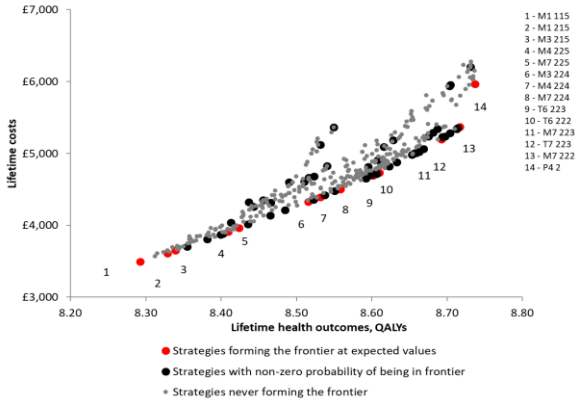
- 11 - M7 223: 0.85 (0.81 to 0.89)
- 12 - T7 223: 0.91 (0.86 to 0.94)
- 13 - M7 222: 0.95 (0.92 to 0.98)
- 14 - P4 2: 1.00 (1.00 to 1.00)



Detailed results

Strategy	% CS cancers detected	%CS cancers diagnosed as non-CS	% non-CS cancers detected	Number of TRUS-biopsies	Number of MRI
M7 223	85%	2%	25%	1.07	1
T7 223	91%	5%	47%	1.42	0.66
M7 222	95%	2%	42%	1.50	1
P4 2	100%	0%	100%	1 + 0.66 TPMB	N/A

Additional cost per QALY gained



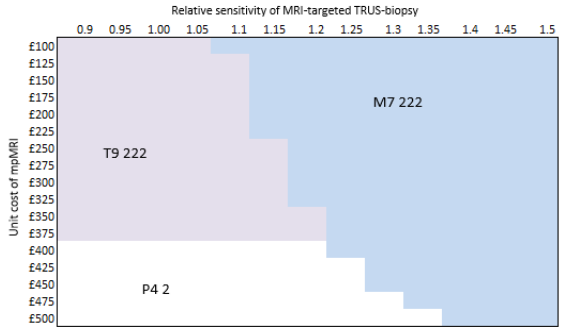
Cost-effectiveness results
M7 223, T7 223, M7 222, P4 2

Strategy	Biopsy definition	mpMRI definition	mpMRI cut-off	QALYs	Costs	ICER
M7: mpMRI for all men; TRUSB in men with suspicion of CS cancer. Re-biopsy with TRUSGB those in whom CS cancer was not detected	2	2	3	8.66	£5021	£5,501
T7: TRUSB for all men; Men classified as NC or non-CS receive a mpMRI. Men with suspicion of CS cancer receive a 2nd TRUSB	2	2	3	8.69	£5194	£5,778
M7: mpMRI for all men; TRUSB in men with suspicion of CS cancer. Re-biopsy with TRUSB those in whom CS cancer was not detected	2	2	2	8.72	£5367	£7,076
P4: TRUSB in all men and TPMB in men in whom CS cancer was not detected	2	Not applicable		8.74	£5968	£30,084

Sensitivity analysis: MRI-targeted TRUS-biopsy

Analysis	Cost-effective strategy at the cost-effectiveness threshold, /QALY gained	
	£20,000	£30,000
Base case	M7 222	M7 222
TSA1: Changes in relative sensitivity of MRI-targeted TRUS biopsy in detecting CS cancer; base-case= 1.2		
between 1-1.10	T9 222	P4 2
between 1.15-1.19	M7 222	P4 2
between 1.20-1.50	M7 222	M7 222
TSA2: Changes in the sensitivity of mpMRI-targeted 2nd TRUS biopsy in detecting CS cancer; base-case = 0.87		
between 0.92-1.00	T9 222	T9 222
Between 0.87-0.92	M7 222	M7 222
Between 0.78 -0.86	M7 222	P4 2
Between 0.67-0.77	P4 2	P4 2

mpMRI cost vs MRI-target TRUS biopsy CE threshold = £20,000/QALY



Findings

- M7 222 is the most cost-effective strategy
  - mpMRI to all men, assessed with cancer definition 2 and cut-off 2
  - Men with suspicion of CS cancer at mpMRI receive a TRUS-biopsy, informed by the imaging scan
  - The (MRI-targeted) TRUS-biopsy is assessed with cancer definition 2.
  - Men in whom the TRUS-biopsy does not detect CS cancer receive a second (MRI-targeted) TRUS-biopsy for confirmation.
- Strategies starting with TRUS-biopsy for all men may be cost-effective if:
  - The relative sensitivity of first MRI-targeted TRUS-biopsy is <1.10;
  - The sensitivity of second MRI-targeted TRUS-biopsy is >0.92;
  - Radical treatment is less cost-effective (higher ICER)
  - >45% of missed CS cancers are diagnosed 1-5 years post referral;
  - Increase in the cost of mpMRI test vs the cost of TRUS-biopsy.

Limitations and key uncertainties (1)
Sensitivity and direct cost of the tests

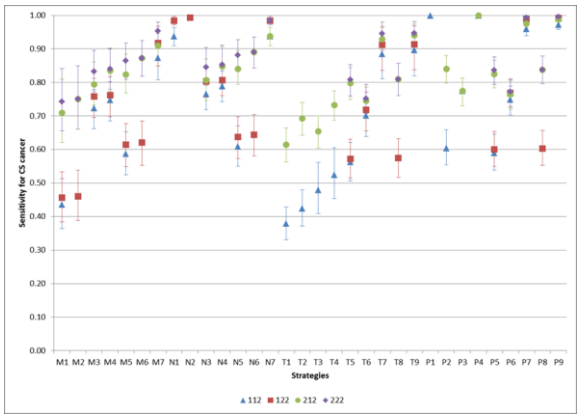
- Limited data on the sensitivity of TRUS-biopsies post-mpMRI → used review by Schoots.
- Aggregated TRUS-biopsy post-MRI as a generic MRI-targeted TRUS-biopsy
- Assumed that TRUS-biopsy post-MRI has the same cost as blind TRUS-biopsy, but has better sensitivity.
  - MRI-targeted TRUS-biopsy has various ways to be implemented, which may have different costs and sensitivity to CS cancers.
- Tests costed with NHS reference costs, which may not reflect true costs to the NHS and lack of capacity to offer mpMRI to all men in a timely basis
- Only included mpMRI, TRUS-biopsy and TPM-biopsy, whilst there are other tests and biomarkers that can be used in diagnosis

Limitations and key uncertainties (2)
Indirect effect on long-term outcomes and costs

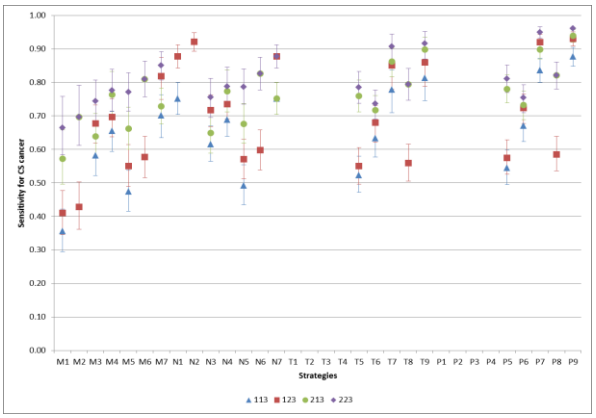
- Summary data on time to progression and death
  - Model is a rough calculation of the comparative costs and health benefits of radical prostatectomy vs watchful waiting.
- No data on progression of men with missed cancers → assumed equivalent to PIVOT's arm on watchful waiting
  - If men's outcomes are worse, more sensitive strategies may be cost-effective.
- No data on NICE active surveillance protocol → assumed equivalent to PIVOT's arm on watchful waiting.
  - If men's outcomes are better, less sensitive strategies may be cost-effective.
- Long-term outcomes relate to men diagnosed with imperfect test (TRUS-biopsy)
  - If men's outcomes are worse, more sensitive strategies may be cost-effective.

Any questions?

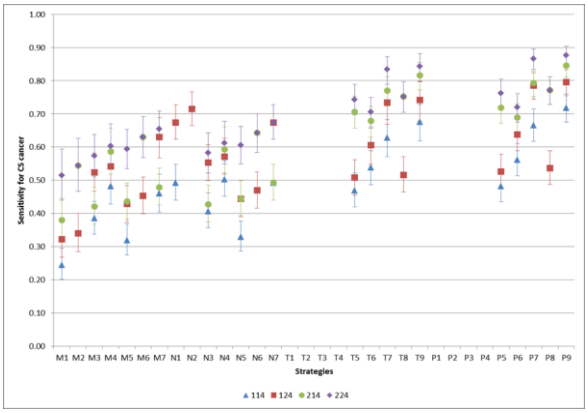
Sensitivity of strategies with mpMRI cut-off 2



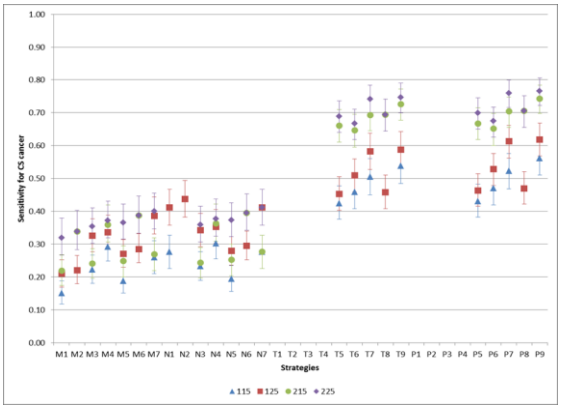
Sensitivity of strategies with mpMRI cut-off 3



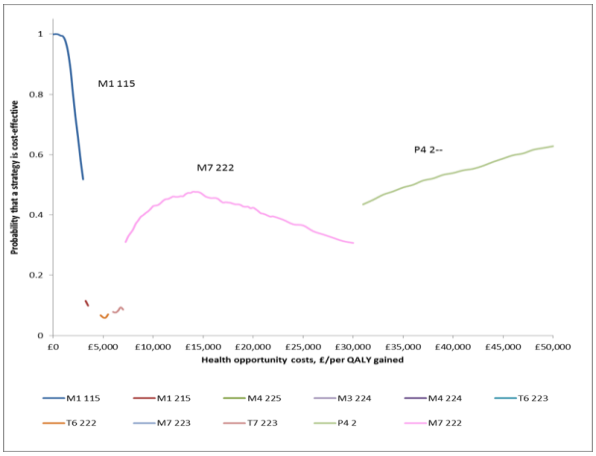
Sensitivity of strategies with mpMRI cut-off 4



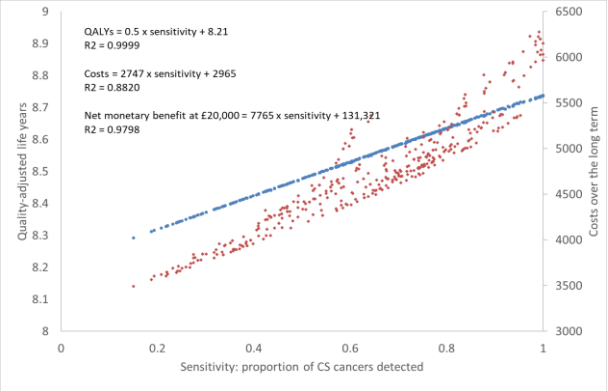
Sensitivity of strategies with mpMRI cut-off 5



What is the option most likely to be cost-effective?

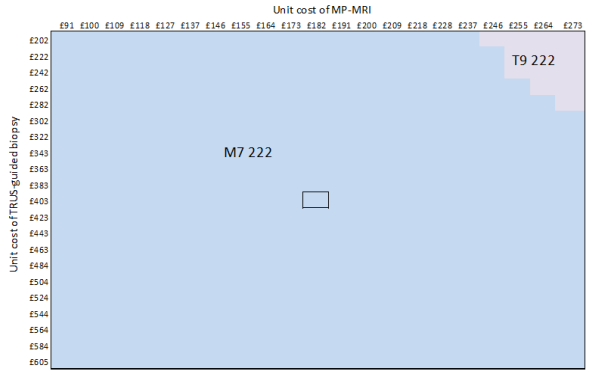


Sensitivity vs. cost-effectiveness results

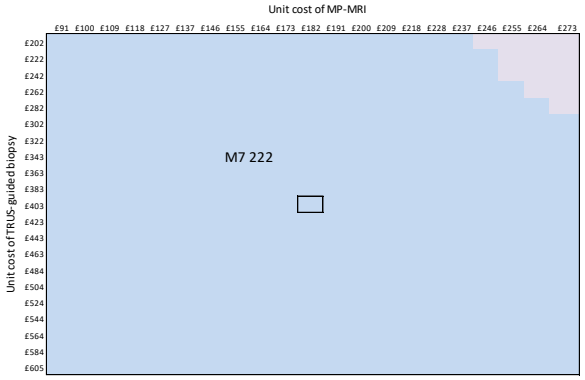


Sensitivity analysis on cost of the tests

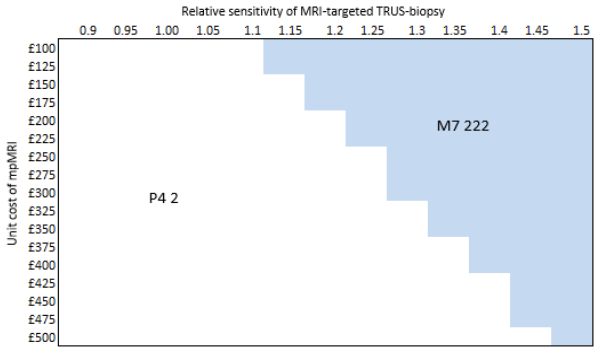
TPM biopsy cost=£1,370
cost-effectiveness threshold=£20,000/QALY



TPM biopsy cost=£1,713
cost-effectiveness threshold=£20,000/QALY



mpMRI cost vs MRI-target TRUS biopsy
CE threshold = £30,000/QALY



Other threshold analyses (1)

Analysis	Cost-effective strategy at the cost-effectiveness threshold	
	£20,000	£30,000
Base case	M7 222	M7 222
Prevalence of intermediate risk vs low risk cancer; base-case=0.53		
between 0.35-0.53	No changes from base-case	
Probability of no cancer; base case=0.28		
between 0.28-0.53	No changes from base-case	
Risk of death from biopsy that changes cost-effective strategy; no risk at base case		
between 0.5-1.0%	P1	P1
risk=1.5%	P1	P1
risk=2%	N2 123	P1
Health-related quality of life impact of TRSU-biopsy		
10% of TPM impact	M7 222	P4 2
60% of TPM impact	M7 222	P1
Same impact	M7 222	M7 222

Other threshold analyses (1)

Analysis	Cost-effective strategy at the cost-effectiveness threshold	
	£20,000	£30,000
Base case	M7 222	M7 222
between 0.5-1.0%	P1	P1
risk=1.5%	P1	P1
risk=2%	N2 123	P1
TSA6: Reduced quality-adjusted survival from incorrect classification as no cancer		
QALY reduction =0.01	M7 222	P4 2--
QALY reduction =0.09	P4 2--	P4 2--
QALY reduction ≥0.1	P4 2--	P4 2--
TSA7: Reduced effectiveness of radical prostatectomy		
Reduced by 10%	M7 222	M7 222
Reduced by 15%	T7 223	M7 222
Reduced by 20%	M1 115	T6 222
TSA8: Impact of repeated testing over time; base-case-0% of men are reclassified in the future		
45%-50%	T9 222	T9 222
50%-100%	T9 222	T9 222

The tests in PROMIS

mpMRI	Standardised MP-MRI with 1·5 Tesla magnetic field strength and a pelvic phased-array coil. T1-weighted, T2-weighted, diffusion-weighted and dynamic gadolinium contrast-enhanced imaging sequences were acquired. Radiology reporting scale: prostates as highly unlikely (1), unlikely (2), equivocal (3), likely (4), and highly likely (5) to harbor CS prostate cancer.
TRUS-biopsy	10–12 core biopsies, with each core identified and processed separately. Reported by uropathologists at each site blinded to the all MR images and TRUS-biopsy findings.
TPM-biopsy	Core biopsies taken every 5 mm and centrally reported at the lead centre (UCLH) by one of two uropathologists blinded to all MR images and TRUS-biopsy findings.