

***Assessment of
mpMRI prostate
diagnostic scans for
diagnosis of prostate
cancer***

September 2016

MSAC application no. 1397

Assessment report

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MSAC's advice does not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

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EXECUTIVE SUMMARY

Main issues for MSAC consideration

- This contracted assessment (CA) investigates the use of multiparameric MRI (mpMRI) in two populations: men with suspected prostate cancer (PCa) (Population 1) and men with low or intermediate risk PCa on active surveillance (AS) programs (Population 2). Currently, these patients are assessed with trans-rectal ultrasound-guided biopsy (TRUSGB) or trans-perineal ultrasound-guided biopsy (TPUSGB).
- No direct evidence on the effectiveness of mpMRI was identified for either population; therefore, a linked evidence approach was used for this assessment.
- The diagnostic accuracy of mpMRI was determined using the bivariate model to generate point estimates of sensitivity and specificity. Overall, Population 1 mpMRI had a sensitivity of 73.4% (95% confidence interval (CI) [57.0, 85.1]) and a specificity of 77.1% (95% CI [63.5, 86.7]) compared to prostate biopsy in the detection of cancer of any severity. Population 2 mpMRI had a sensitivity of 79.3% (95% CI [74.6, 83.3]) and a specificity of 55.1% (95% CI [50.4, 59.8]) compared to prostate biopsy. Therefore, mpMRI misses PCa that would be accurately diagnosed by biopsy.
- Our analysis found no statistical difference in the sensitivity and specificity of mpMRI in the detection of cancer of any severity compared to clinically significant cancer.
- To limit sources of uncertainty, only studies with no applicability issues and those using a consistent threshold were included. Despite this, for Population 1 there is considerable uncertainty in the point estimates as evidenced by wide confidence intervals (ranging from 9.5 to 14.5 points around the estimate). Subgroup analysis was conducted to explore the cause of this heterogeneity; however, no source was identified. There may be reliability issues with the use of mpMRI and the Prostate Imaging Reporting and Data System (PI-RADS). For Population 2 there is a high level of certainty in the point estimates of sensitivity and specificity.
- For low-concern patients, the implication of a false negative mpMRI is delayed treatment; this does not appear to adversely affect patient outcomes for the majority of patients.
- For low-concern patients the consequence of a true negative (and false negative) is an avoided biopsy. Biopsy is associated with rare but potentially serious adverse events whereas mpMRI is generally considered safe. Avoided biopsy will eliminate the risk of major infection and associated re-hospitalisation for 1-2% of patients receiving trans-rectal biopsy.
- High-concern patients will have a biopsy regardless of mpMRI results and there is no change in therapeutic effectiveness associated with the introduction of mpMRI for these patients.
- The cost-effectiveness of mpMRI differs between Population 1 and Population 2. In Population 1, mpMRI is dominated by prostate biopsy. In Population 2, the incremental cost of mpMRI is \$12,821 per quality of life year (QALY) gained in the base-case.

Main issues for MSAC consideration

- The current assessment was performed in parallel with the evaluation of MRI-guided biopsy (MRIGB) procedures for diagnosis of PCa (CA 1424). It was therefore not known yet if (any type of) MRIGB would be part of the future clinical management algorithm. The proposed clinical management algorithm included the use of MRIGB after mpMRI for patients with PI-RADS 4-5. In the base-case, mpMRI was evaluated assuming no change in the type of biopsies used (i.e. 75% TRUSGB, 25% TPUSGB). The impact of introducing MRIGB in the intervention arm was evaluated in a sensitivity analysis and increased the incremental cost effectiveness ratio from \$12,821 to \$66,320 per QALY gained.
- Seventeen ongoing clinical trials were identified (Appendix I) indicating considerable additional research may be available on this topic in the future.

ASSESSMENT OF mpMRI PROSTATE DIAGNOSTIC SCANS FOR DIAGNOSIS OF PROSTATE CANCER

This contracted assessment examines the evidence to the support listing of multiparametric MRI (mpMRI) prostate diagnostic scans on the Medicare Benefits Schedule (MBS). The service would be used for cancer detection in patients with suspicion of prostate cancer (PCa) and disease monitoring in patients with known disease who are on active surveillance programs (AS). The target populations are men with suspicion of PCa (Population 1) and men diagnosed with low or intermediate risk PCa undertaking AS (Population 2).

ALIGNMENT WITH AGREED PROTOCOL

This contracted assessment of mpMRI prostate diagnostic scans addresses all of the Population, Intervention Comparator, Outcomes (PICO) elements that were pre-specified in the protocol ratified by the Protocol Advisory Sub-Committee (PASC) or the Medical Services Advisory Committee (MSAC) Executive.

PROPOSED MEDICAL SERVICE

In mpMRI three magnetic pulse sequences: T2 weighted (T2W), diffusion weighted image (DWI), and dynamic-contrast enhanced (DCE), are combined to form images that are analysed together.

Images are scored using the Prostate Imaging Reporting and Data System (PI-RADS) v2 scoring system. This five-point scale indicates the likelihood that mpMRI findings correlate with the presence of clinically significant cancer at a particular location in the prostate, where 1 = very low (clinically significant PCa is highly unlikely to be present) and 5 = very high (clinically significant PCa is highly likely to be present).

In low-concern patients (no family history, free/total prostate-specific antigen (PSA) >12 per cent and PSA density <0.15), if the findings of mpMRI are suspicious (PI-RADS 4 or 5), a confirmatory biopsy is taken to verify the presence or absence of cancer. High-concern patients receive a biopsy regardless of the results of the mpMRI.

Currently there is no MBS item for mpMRI prostate diagnostic scan; as such, it is not currently reimbursed via the MBS. In addition, no data on the use of mpMRI in the public health system in Australia was identified. It is not clear to what extent mpMRI is currently being used for patients in either population.

PROPOSAL FOR PUBLIC FUNDING

The item descriptors for the proposed services are shown in Table 1. These are unchanged from those in the PASC ratified protocol.

Table 1 Proposed MBS item descriptor

Category 5 – Diagnostic Imaging Services
<p>MBS [item number] Multiparametric Magnetic Resonance Imaging (mpMRI) performed under the professional supervision of an eligible provider at an eligible location where the patient is referred by an urologist, radiation oncologist, or medical oncologist and where:</p> <ul style="list-style-type: none"> a) a standardised image acquisition protocol involving T2 weighted imaging, Diffusion Weighted Imaging, and Dynamic Contrast Enhancement (unless contraindicated) is used; and b) the man is suspected of having prostate cancer on the basis of a high or concerning PSA. <p>Scan of the prostate for: – detection of cancer (R)(Contrast)</p> <p>Fee: [Applicant advises that current fee charged is \$600] [Relevant explanatory notes]</p>
<p>MBS [item number] Multiparametric Magnetic Resonance Imaging (mpMRI) performed under the professional supervision of an eligible provider at an eligible location where the patient is referred by an urologist, radiation oncologist, or medical oncologist and where:</p> <ul style="list-style-type: none"> a) a standardised image acquisition protocol involving T2 weighted imaging, Diffusion Weighted Imaging, and Dynamic Contrast Enhancement (unless contraindicated) is used; and b) the man has an existing diagnosis of low or intermediate risk prostate cancer and is undertaking Active Surveillance. <p>Scan of the prostate for: – assessment of cancer (R)(Contrast)</p> <p>Fee: [Applicant advises that current fee charged is \$600] [Relevant explanatory notes]</p>

POPULATION

In 2012, there were 20,065 new cases of PCa diagnosed in Australia and the age-standardised incidence rate was 163 cases per 100,000 males. Data indicates that 15.3 per cent of patients newly diagnosed with PCa are undertaking AS to manage their disease.

This assessment considers the use of mpMRI in the following two populations:

1. men who are suspected of having PCa on the basis of a high or concerning PSA; and
2. men diagnosed with low or intermediate risk PCa undertaking AS.

COMPARATOR DETAILS

Within current Australian practice, the signs of PCa are detected using a prostate-specific antigen test (PSA test) and/or a digital rectal examination (DRE). However, these are not diagnostic tests. The diagnosis of PCa is obtained using either Trans-rectal Ultrasound Guided Biopsy (TRUSGB), or Trans-perineal Ultrasound Guided Biopsy (TPUSGB).

The PASC ratified Protocol states, for men who are suspected of having PCa because of a high or concerning PSA, the comparators are:

1. PSA/DRE + clinical judgement and TRUSGB or TPUSGB
2. PSA/DRE + clinical judgement alone, for patients who elect not to undergo TRUSGB or TPUSGB.

For men diagnosed with low or intermediate risk PCa undertaking AS, the comparator is the current AS protocol with repeat TRUSGB or TPUSGB.

During a biopsy, a needle is inserted trans-rectally or trans-perineally into the prostate under ultrasound, MRI, or cognitive guidance, and a set of random samples of tissue (using between 12-36 needles) are taken from the prostate. The samples are analysed under a microscope, to ascertain if cancer cells are present. Cancers of the prostate are graded using the Gleason system, a score of 6 or less is considered low risk, a score of 7 is considered intermediate risk, and a score of 8 or above is considered to be high risk.

The reference standard for this assessment is pathology of prostate samples collected via biopsy.

CLINICAL MANAGEMENT ALGORITHM(S)

Population 1

The signs of PCa are currently detected using a PSA test and/or a DRE. Criteria for suspected PCa, for the purposes of this contracted assessment, are defined as:

- PSA greater than 3ng/ml (or lower level if less than 50 years of age); or
- Positive family history (includes breast cancer [BRCA] gene mutation); or
- Free/total PSA ratio less than 25 per cent; or
- Positive DRE.

As stated previously, PSA and DRE are not diagnostic and diagnosis is obtained via either TRUSGB or TPUSGB. Patients who receive a negative biopsy result remain under observation and have a follow-up PSA test after six months. Patients with a biopsy result indicating intermediate or low risk cancer

are offered AS. Patients with a biopsy result indicating high or intermediate risk cancer are offered surgery or radiotherapy/hormone therapy combinations. Please see Figure 1, Section A for the current clinical algorithm.

Under the proposed clinical management algorithm, patients with suspected PCa would be imaged using mpMRI. Please see Figure 2, Section A for the proposed clinical algorithm.

Patients with PI-RADS scores 1, 2, or 3 with low-concern, will return to primary care and may remain under observation. These patients will avoid a biopsy under the proposed algorithm. Patients with PI-RADS score of 1, 2, or 3 with very high- or intermediate-concern will have a systematic biopsy under both the current and proposed algorithms. Patients with PI-RADS scores 4 or 5, regardless of clinical concern, will have an MRI guided biopsy (MRIGB) in place of a systematic biopsy under current management. High- or intermediate-concern is defined as:

- Positive family history (includes BRCA gene mutation); or
- Free/total PSA ratio less than 12 per cent; or
- PSA density (PSA number divided by prostate volume) greater than 0.15.

Low-concern is defined as patients who have suspected PCa but do not meet the criteria for high- or intermediate-concern.

The impact of the change in management from TRUSGB and/or TPUSGB to MRIGB is the subject of another contracted assessment (MSAC application number 1424[CA 1424]).

Population 2

Men who have a diagnosis of intermediate or low risk cancer may choose to undertake AS. During AS, men undergo annual scheduled testing (PSA, PSA kinetics and DRE) over a period of five years or more. Those on AS also have scheduled prostate biopsies at 12 months and then every three years thereafter. If there is concern about clinical or PSA/DRE changes, men may opt to have an additional prostate biopsy. Based on the results of these biopsies, men will either continue on AS or be offered surgery or a radiotherapy/hormone therapy combination for their cancer. The full details of the current AS protocol are set out in Figure 3, Section A.

If the proposed mpMRI service is added to the AS protocol, it will be used as an additional test prior to prostate biopsy. Men who are due for their scheduled biopsy and men who have concern about clinical or PSA/DRE changes would first have an mpMRI scan. The criteria for concern are the same as for Population 1 (PSA greater than 3ng/ml or lower level if less than 50 years of age, positive family history or free/total PSA ratio less than 25%). Men with PI-RADS scores 1, 2, and 3 with low-concern will return to AS and avoid biopsy under the proposed algorithm. Men with intermediate/high-concern and men with low-concern and a PI-RADS score of 4-5 will continue with a re-biopsy. Patients with a PI-RADS score of 4-5 would have an MRIGB, while patients with a PI-

RADS score of 1-3 (high- or intermediate-concern) would have a systematic biopsy. Based on the results of these biopsies, men will either continue on AS or be offered surgery or a radiotherapy/hormone therapy combination for their cancer. The details of the proposed protocol for AS are presented in Figure 4, Section A.

The impact of the change in management from TRUSGB to MRIGB is the subject of another contracted assessment (CA 1424).

KEY DIFFERENCES IN THE DELIVERY OF THE PROPOSED MEDICAL SERVICE AND THE MAIN COMPARATOR

Indications for both mpMRI scan of prostate and biopsy of prostate include men with suspicious findings on PSA/DRE test with suspected PCa or men diagnosed with low or intermediate risk PCa undertaking AS. There are no differences in the patient indications for the index and comparator tests.

The risk profiles for mpMRI and biopsy (any type) differ due to the nature of the techniques as mpMRI is non-invasive imaging technique and biopsy is an invasive procedure.

MRI is an established technique, the likelihood of adverse events is very low, the severity of adverse events is generally low, and MRI is considered safe for almost all patients.

Different biopsy techniques may have different risk profiles. For any trans-rectal biopsy, the main risk is infection due to the insertion of needles through the rectum, which is a non-sterile environment. At its most severe, infection may cause sepsis and death although this is very rare. Antibiotic prophylaxis and pre-biopsy workup including enema may reduce the risk of infection. Other complications of prostate biopsy include bleeding (haematuria, haemospermia, and hematochezia), urinary tract infection (UTI), and urinary obstruction. In trans-perineal biopsy, risk of infection is lower due to the needles being inserted in the perineum, which is a sterile environment. Trans-perineal biopsy also results in less rectal bleeding while the incidence of other adverse events is consistent with TRUSGB.

CLINICAL CLAIM

The clinical claim is that mpMRI scans of the prostate have better diagnostic accuracy (hence, are more effective) and are safer than the current approach. In the event that claims of superior efficacy and safety are supported by the literature, a cost-utility analysis would be appropriate.

APPROACH TAKEN TO THE EVIDENCE ASSESSMENT

The medical literature was searched on 20 May 2016 to identify relevant studies. The search was not date limited. Databases searched include EMBASE, PubMed, Cochrane Database of Systematic Reviews and York CRD. A linked evidence approach was taken to the analysis (Table 2).

CHARACTERISTICS OF THE EVIDENCE BASE

A total of 33 primary studies, including 6,606 patients, that assessed the diagnostic accuracy of mpMRI against prostate biopsy in patients with a concerning PSA or DRE result were identified. Sixteen primary studies, including 1,367 patients, that assessed the diagnostic accuracy of mpMRI against prostate biopsy in patients eligible for AS programs were identified.

Table 2 Key features of the included linked evidence

Type of evidence	Description	Number ^b
Comparative diagnostic performance ^a	Diagnostic studies of test accuracy and studies comparing mpMRI to TRUSGB or TPUSGB (reference standard) in the same group of patients were identified for both populations. No diagnostic case control or diagnostic yield studies were included.	Population 1: k=10 n=2,062 Population 2: k=6 n=820
Therapeutic efficacy	No studies were identified that assessed change in management associated with mpMRI. Change in management for low-concern patients with a negative mpMRI is dictated by the clinical algorithm – these patients will avoid biopsy. Low-concern patients with a positive mpMRI and all high-concern patients will undergo biopsy – results from biopsy inform management decisions. An assessment of prostate biopsy is being undertaken in MSAC Application CA 1424; the Assessment Group for that application has advised no change in management studies were identified.	k=0 n=0
Therapeutic effectiveness	Retrospective cohort studies were identified that assessed the impact of delayed treatment in patients with diagnosed PCa were used to inform therapeutic effectiveness.	Systematic reviews: k=1 n=34,517 Primary studies k=6 n=32,504

^a: Reference standard available. ^b k refers to the number of studies, n refers to the number of patients.

PCa = prostate cancer, CA = contracted assessment, mpMRI = multiparametric MRI, MRI = magnetic resonance imaging, TRUSGB = trans-rectal ultrasound guided biopsy, TPUSGB = trans-perineal ultrasound guided biopsy.

For the meta-analyses on diagnostic accuracy, only studies that were applicable to the proposed usage of mpMRI in Australia were included. Results from this subgroup of key studies were used to inform the therapeutic effectiveness and economic models. No gaps in the literature were identified.

RESULTS

Safety

Test adverse events

No adverse event associated with mpMRI was identified in the literature.

Comparator adverse events

Trans-rectal Biopsy

The evidence base for assessing the safety of trans-rectal prostate biopsy consists of nine case series (Level IV studies), six comparative studies with controls (Level III-2), one comparative study with historical control (Level III-3), two randomised controlled trials, and one systematic review.

Nine studies reported patient re-hospitalisation ranges from 0.4 to 5.5 per cent. Eight studies reported major patient infection ranges from 0.2 to 2.4 per cent. Nine studies reported minor patient infection ranges from 0.7 to 6.9 per cent. Thirteen studies reported that the patient incidence of bleeding related events (haematuria, hematochezia, or haemospermia) ranges from 0.8 to 88.0 per cent. Twelve studies reported patient urinary obstruction or difficulty voiding ranges from 0.8 to 21.0 per cent.

Although uncommon, two deaths reported in the literature due to sepsis resulting from a trans-rectal biopsy-related infection.

Trans-perineal Biopsy

Three studies were identified that assessed the safety of trans-perineal biopsies, one large case series and two systematic reviews.

Hospitalisation after TPUSGB ranged from 0.7 to 2.1 per cent in the literature. In the case series study 3,007 patients underwent trans-perineal prostate biopsy in a single centre from 2003 to 2013, total rates of complications, including those not requiring hospitalisation, were major infection 0.03 per cent, acute urinary obstruction 1.9 per cent, urethral bleeding 0.1 per cent, haematuria 47.0 per cent, haemospermia 6.1 per cent, and perineal haematoma 0.5per cent.

In the studies reported in two systematic reviews, urinary obstruction ranged from 0.5 to 20.6 per cent, significant haematuria 0.3 to 57.0 per cent, mild/transient haematuria 3.7 to 45.3 per cent, UTI 1.1 to 8.9 per cent, and fever 0.5 to 5.3 per cent of patients. The majority of studies reported that no infection occurred.

There is no evidence in the literature of deaths related to trans-perineal prostate biopsy.

Adverse events from change in management

The only identified change in management associated with the proposed clinical algorithm is an avoidance of biopsy with a negative mpMRI result. Therefore, change in management is associated with the avoidance of the adverse events for biopsy described above.

Effectiveness

Direct effectiveness

No studies were identified that assessed the direct evidence of mpMRI in either population.

Effectiveness from linked evidence

1. Accuracy

Ten studies, including 2,062 patients, were identified that reported a per-patient analysis of the diagnostic accuracy of mpMRI in patients suspected of having PCa because of concerning PSA or DRE results. Pathology of samples obtained by biopsy was the reference standard in all studies. There were no applicability issues identified between the included key studies and the proposed population in the Protocol. Only studies using a consistent threshold for PI-RADS scoring as stated in the Protocol (\geq PI-RADS 4 for a positive result) were included in this analysis.

The reference standard used in the diagnostic accuracy studies was biopsy (TRUSGB, TPUSGB or cognitive MRIGB with TRUSGB). It is recognised that biopsy is not a perfect reference standard; however, this was used in all of the included studies. Two systematic reviews, Schoots et al. (2015) and Shen et al. (2012) reported that the diagnostic accuracy of TRUSGB, TPUSGB and MRIGB are statistically equivalent. Summary statistics for Population 1 and Population 2 are provided in Table 3 and Table 4.

Table 3 Summary statistics for mpMRI against biopsy (TRUSGB, TPUSGB or cognitive MRIGB) in Population 1 (assumed disease prevalence of 35% for low-concern patients and 50% for high-concern patients)

Accuracy	mpMRI – all cancer (n=2,062, k=10)	Clinically significant cancer (n=1,229, k=6)
Sensitivity, % [95% CI]	73.4 [57.0, 85.1]	76.3 [58.6, 88.0]
Specificity, % [95% CI]	77.1 [63.5, 86.7]	82.9 [71.5, 90.4]
PPV, % [95% CI]	77.2 [63.4, 86.8]	74.7 [69.4, 79.3]
NPV, % [95% CI]	72.8 [57.2, 84.2]	83.5 [78.8, 87.4]

PPV = positive predictive value, NPV = negative predictive value, mpMRI = multiparametric MRI, MRI = magnetic resonance imaging, CI = confidence interval.

Identified evidence does not show that the diagnostic accuracy of mpMRI differs in the detection of any type of PCa compared to the detection of clinically significant cancer. Therefore, results for the detection of any cancer have been used to inform the therapeutic effectiveness and economics sections of this report.

The point estimates for sensitivity and specificity are associated with wide confidence intervals reflecting uncertainty in the results. Heterogeneity in the evidence base is high, particularly for studies reporting the diagnosis of any cancer; and unable to be explained through subgroup analysis of clinical features.

An assessment of the reliability of mpMRI found Kappa values for inter-reader agreement ranged from 0.34 to 0.81. Results from key diagnostic accuracy studies were consistent with results from studies seeking to measure the inter-reader reliability of mpMRI using PI-RADS. The results suggest

reliability may be an issue with mpMRI and this may therefore explain the observed heterogeneity in the estimates of sensitivity and specificity.

The quality for the diagnostic accuracy outcomes was rated as ‘poor’ using the GRADE tool. This reflects the serious issues with imprecision and inconsistency in the evidence base.

Table 4 Summary statistics for mpMRI against biopsy (TRUGB, TPUSGB or cognitive MRIGB) in Population 2 (prevalence of disease upgrade of 30%)

Accuracy	mpMRI (n=820, k=6)
Sensitivity, % [95% CI]	79.3 [74.6, 83.3]
Specificity, % [95% CI]	55.1 [50.4, 59.8]
PPV	59.4 [53.5, 65.0]
NPV	76.2 [70.1, 81.4]

PPV = positive predictive value, NPV = negative predictive value, mpMRI = multiparametric MRI, MRI = magnetic resonance imaging, CI = confidence interval.

2. Therapeutic efficacy (change in management)

The change in management associated with changing from a TRUSGB or TPUSGB to an MRIGB is the subject of CA 1424. The Assessment group for CA 1424 advised that no studies have been identified that investigate this change in management. Based on systematic review evidence, there is no difference in diagnostic accuracy between the biopsy techniques (this assumption is discussed in Sections B5.1 and B5.2 of the report). Therefore, for both populations, it is assumed due to the equivalent accuracy that there will be no overall change in management associated with changes to biopsy type.

Population 1

The clinical algorithm indicates that patients with low-concern of developing PCa will be managed differently to those with high-concern of PCa (see Figures 1-4, Section A). Following is a summary of the expected change in management resultant from the introduction of mpMRI

Low-concern patients (estimated to be 50% of patients in Population 1)

mpMRI True positive: Change from TRUSGB or TPUSGB to MRIGB. No evidence that patients with a true positive will experience any change in management or change to health outcomes was identified.

mpMRI False positive: Change from TRUSGB or TPUSGB to MRIGB. No evidence that patients with a false positive will experience any change in management or change to health outcomes was identified.

mpMRI True negative: Change from TRUSGB or TPUSGB to no biopsy. These patients will avoid having a biopsy and therefore avoid any potential biopsy-related adverse events as discussed above in the 'Safety' section.

mpMRI False negative: Change from TRUSGB or TPUSGB to no biopsy. These patients will avoid having a biopsy and therefore avoid any potential biopsy-related adverse events as discussed above in the 'Safety' section. However, the patients will be subject to a delay in the diagnosis of their disease. The impact of delayed treatment is discussed below ('Therapeutic effectiveness' section).

High-concern patients (estimated to be 50% of patients in Population 1)

All high-concern patients will undergo a biopsy (change from TRUSGB or TPUSGB to MRIGB). No evidence that patients who undergo a biopsy of any type will experience any change in management or change to health outcomes was identified.

Population 2

Low-concern patients (estimated to be 85% of patients in Population 2)

mpMRI True positive: Change from TRUSGB or TPUSGB to MRIGB. No evidence that patients with a true positive will experience any change in management or change to health outcomes was identified.

mpMRI False positive: Change from TRUSGB or TPUSGB to MRIGB. No evidence that patients with a false positive will experience any change in management or change to health outcomes was identified.

mpMRI True negative: Change from TRUSGB or TPUSGB to no biopsy. These patients will avoid having a biopsy and therefore avoid any potential biopsy-related adverse events as discussed above in the 'Safety' section.

mpMRI False negative: Change from TRUSGB or TPUSGB to no biopsy. These patients will avoid having a biopsy and therefore avoid any potential biopsy-related adverse events as discussed above in the 'Safety' section. However, the patients will be subject to a delay in the upgrading of their disease. The impact of delayed treatment is discussed below (Therapeutic effectiveness section).

High-concern patients (estimated to be 15% of patients in Population 2)

All high-concern patients will undergo a biopsy. No evidence that patients who undergo a biopsy of any type will experience any change in management or change to health outcomes was identified.

3. Therapeutic effectiveness (health benefit from change in management)

Population 1

The health outcomes associated with delayed treatment due to a false negative mpMRI result in Population 1 are summarised in Table 5.

Table 5 Population 1: Summary of findings for the linked evidence comparison of mpMRI, relative to TRUSGB or TPUSGB, in patients at low-concern with suspected prostate cancer with assumed pre-test probability (prevalence) of 35%

Outcomes	Patients/ Studies	Quality of evidence ^a	No. per 100 patients with intervention [95% CI] ^b	No. per 100 patients with comparator ^c [95% CI]	Importance	Comments
True positives	2,062 patients (10 studies).	⊕⊕⊖⊖	26 [20, 30]	28 [25, 31]	Critical	Will undergo biopsy as under current management.
False positives	2,062 patients (10 studies).	⊕⊕⊖⊖	15 [9, 24]	0 [0, 0]	Critical	Will undergo biopsy as under current management.
True negatives	2,062 patients (10 studies).	⊕⊕⊖⊖	50 [41, 56]	65 [65, 65]	Critical	Will avoid the potential adverse events resultant from biopsy.
False negatives	2,062 patients (10 studies).	⊕⊕⊖⊖	9 [5, 15]	7 [4, 11]	Critical	Will avoid the potential adverse events resultant from biopsy but possible detriment due to delayed treatment.
Major Infection	45,492 patients (8 studies).	⊕⊕⊖⊖	0	TRUSGB: Range 0-2 TPUSGB: 0	Critical	-
Minor infection	132,239 patients (9 studies).	⊕⊕⊖⊖	0	TRUSGB: Range 0-7 TPUSGB: Range 0-1	Critical	-
Re-hospitalisation	292,956 patients (9 studies).	⊕⊕⊖⊖	0	TRUSGB: Range 0-6 TPUSGB: Range 1-2	Critical	-
Bleeding	334,688 patients (13 studies).	⊕⊖⊖⊖	0	TRUSGB: Range 1-88 TPUSGB: Range 1-6	Important	-
Urinary obstruction	132,020 patients (12 studies).	⊕⊖⊖⊖	0	TRUSGB: Range 1-21 TPUSGB: Range 0-38	Important	-
Overall survival	41,146 patients (5 studies).	⊕⊖⊖⊖	NA	NA	Critical	Delay did not impact overall survival (results from 5 studies).

Outcomes	Patients/ Studies	Quality of evidence ^a	No. per 100 patients with intervention [95% CI] ^b	No. per 100 patients with comparator ^c [95% CI]	Importance	Comments
Cancer-free survival	8,916 patients (2 studies).	⊕⊕⊕⊕	NA	NA	Critical	Delay did not impact cancer free survival (results from 2 studies).
Rate of metastases formation	6,681 patients (4 studies).	⊕⊕⊕⊕	NA	NA	Critical	Delay did not impact rate of metastases formation (results from 4 studies).
Rate of biochemical recurrence	19,768 patients (14 studies).	⊕⊕⊕⊕	NA	NA	Critical	3 studies reported recurrence was associated with delayed treatment, 11 studies reported no impact.
Rate of extra capsular extension	16,039 patients (7 studies).	⊕⊕⊕⊕	NA	NA	Important	Delay did not impact rate of extra-capsular extension (results from 7 studies).
Rate of lymph node involvement	3,605 patients (3 studies).	⊕⊕⊕⊕	NA	NA	Important	Delay did not impact rates of lymph node involvement (results from 3 studies).
Rate of positive surgical margins	14,413 patients (6 studies).	⊕⊕⊕⊕	NA	NA	Important	1 study reported a delay >9 months was associated with increase in rate of positive surgical margins (intermediate risk disease only). 5 studies reported no impact from delay.

^a: GRADE Working Group grades of evidence (Guyatt et al. 2013)

⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.

⊕⊕⊕⊕ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

⊕⊕⊕⊕ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

⊕⊕⊕⊕ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

^b: A prevalence of PCa in low-concern patients of 30-40% was provided by the Applicant (Applicant 2016). The midpoint of this range has been used to inform these estimates. Only low-concern patients have been included in this assessment as there is no change in management for patients at high-concern, regardless of mpMRI results.

^c: Calculated using the reported sensitivity of TRUSGB biopsy of 0.81 (95% CI [0.70, 0.88]) and assuming TRUSGB had a specificity of 100%.

NA = not applicable, CI = confidence interval, TRUSGB = trans-rectal ultrasound guided biopsy, TPUSGB = trans-perineal ultrasound guided biopsy.

Low-concern patients who receive a false negative mpMRI will experience a delay to treatment; it is not clear that this delay is associated with any adverse outcomes for patients, particularly for patients with low risk disease. However, the evidence base to inform patient outcomes following delayed treatment is considered very low quality and is based on observational studies.

While it is possible mpMRI has inferior diagnostic accuracy compared to TRUSGB/TPUSGB, there is evidence that this may not adversely affect patients' outcomes. On the basis of the evidence profile (Table 5), it is suggested that, relative to TRUSGB or TPUSGB, that mpMRI imaging has non-inferior effectiveness. However, the uncertainty associated with the diagnostic accuracy of mpMRI should be taken into account.

Based on avoidance of harms associated with biopsy under the proposed algorithms, it is suggested mpMRI has superior safety to TRUSGB; however, the adverse events associated with biopsy are generally minor and occur in a small proportion of patients.

Population 2

The health outcomes associated with delayed treatment due to a false negative mpMRI result in Population 2 are summarised in Table 6.

Table 6 Population 2: Summary of findings for the linked evidence comparison of mpMRI, relative to TRUSGB or TPUSGB, in patients on active surveillance with assumed pre-test probability (prevalence) for upgraded disease of 30%

Outcomes	Patients/ Studies	Quality of evidence ^a	No. per 100 patients with intervention [95% CI] ^b	No. per 100 patients with comparator [95% CI] ^c	Importance	Comments
True positives	820 patients (6 studies).	⊕⊕⊕⊕	24 [22, 35]	28 [25, 31]	Critical	Will undergo biopsy as under current management.
False positives	820 patients (6 studies).	⊕⊕⊕⊕	31 [28, 37]	0 [0, 0]	Critical	Will undergo biopsy as under current management.
True negatives	820 patients (6 studies).	⊕⊕⊕⊕	39 [35, 42]	65 [65, 65]	Critical	Will avoid the potential adverse events resultant from biopsy.

Outcomes	Patients/ Studies	Quality of evidence ^a	No. per 100 patients with intervention [95% CI] ^b	No. per 100 patients with comparator [95% CI] ^c	Importance	Comments
False negatives	820 patients (6 studies).	⊕⊕⊕⊕	6 [5, 8]	7 [4, 11]	Critical	Will avoid the potential adverse events resultant from biopsy but possible detriment due to delayed treatment.
Positive surgical margins	219 patients (1 study).	⊕⊖⊖⊖	NA	NA	Important	There is no evidence that delayed treatment increases the rate of positive surgical margins.

^a: GRADE Working Group grades of evidence (Guyatt et al. 2013)

⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.

⊕⊕⊕⊖ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

⊕⊕⊖⊖ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

⊕⊖⊖⊖ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

^b: A prevalence of PCa upgrade in low-concern patients of 30% was provided by the Applicant (Applicant 2016). Only low-concern patients have been included in this assessment as there is no change in management for patients at high-concern, regardless of mpMRI results.

^c: Calculated using the reported sensitivity of TRUSGB biopsy of 0.81 (95% CI [0.70, 0.88]) and assuming TRUSGB had a specificity of 100%.

NA = not applicable, mpMRI = multiparametric MRI, CI = Confidence interval.

Only patients with low-concern who have a negative mpMRI will have a change in management under the proposed algorithm. These patients will avoid a biopsy. Advice from the Applicant is that the prevalence of upgraded disease in these patients is 30 per cent.

Patients who have a false negative mpMRI will have their treatment delayed and remain on AS. One observational study was identified that assessed the impact of delayed treatment in this population and the quality of evidence was rated very low using the GRADE tool. On this basis, mpMRI is considered non-inferior to TRUSGB or TPUSGB.

The relative safety of mpMRI and biopsy are discussed above for Population 1. There is no evidence that the relative harms associated with mpMRI and biopsy will be any different in Population 2 than those described above for Population 1; therefore, mpMRI is advised to have superior safety.

TRANSLATION ISSUES

Applicability issues

Comparison of population and intervention characteristics between the key clinical studies and Australian registry data did not identify overt applicability issues. To ensure applicability of the test accuracy results to the intended MBS population, only studies using PI-RADS ≥ 4 as a cut-off were included.

In Population 1, differences in patient pre-selection for mpMRI may impact tumour characteristics and therefore test accuracy. According to the proposed clinical algorithm in the Protocol, the expected MBS population will be pre-selected before undergoing mpMRI (PSA $>3\text{ng/ml}$ or lower level if <50 years of age, or positive family history, or free/total ratio $<25\%$). From most of the key clinical studies it was not clear whether the study populations would meet these criteria. To address this uncertainty, sensitivity analyses were performed to evaluate the impact of the reduced and increased test accuracy on the cost-effectiveness of mpMRI. Sensitivity analyses were also performed to evaluate the sub selection of Australian studies only.

In Population 2, the patient characteristics in key clinical studies are similar to the expected MBS population with low to intermediate risk cancer, based on Australian registry data. However, the Australian active surveillance population has a higher proportion of men with intermediate and high risk cancer. Given their different characteristics, the mpMRI accuracy results may not be applicable to this population at higher risk of cancer progression. It should be noted that high risk men are not eligible for active surveillance with mpMRI according to the Protocol.

For both Population 1 and 2, mpMRI accuracy may be conditional on the experience of the reader and the key studies generally used experienced readers. There is a lack of information on both the potential learning curve and the experience levels of Australian mpMRI readers. To address this issue a sensitivity analysis was performed to evaluate the impact of the reduced and increased accuracy on the cost-effectiveness of mpMRI.

Extrapolation issues

None of the key accuracy studies discussed in section B measured the impact of mpMRI on prostate cancer progression and/or mortality. Prognostic information was sourced from other literature, aligning with the sources used in the evaluation of MR-guided biopsy procedures for diagnosis of PCa (CA 1424). The following probabilities were used: probability of developing cancer whilst receiving PSA screening (9.7%), probabilities of prostate cancer progression (8.8% for upstaging while under active surveillance, 2.6% for further progression to advanced prostate cancer), probability of prostate cancer death (0.6% for patients with localised disease, 22% for patients with advanced disease). Australian Bureau of Statistics (ABS) life tables were used to calculate age-related background mortality.

Both for false negatives and false positives, the error was assumed to be corrected without a negative impact on prognosis. This assumption was made due to insufficient evidence to support an impact of treatment delay on disease progression and mortality. A sensitivity analysis evaluates the

potential impact of assuming an increased risk of disease progression for the subgroup of high risk PCa patients who experience treatment delay due to false negative prognosis.

Transformation issues

Data pertaining to quality of life were not collected in the studies presented in Section B. Utility values for the economic evaluation were therefore obtained from literature (see Table 45) and aligned with the values used in the parallel application for MRI guided biopsy CA 1424.

Table 7 Utility values used in the economic model

Health state	Utility value, mean (SD) [95%CI]
General Australian population of males aged 61 – 70y	0.82 (NR) (0.80–0.84)
low/intermediate risk PCa on active surveillance	0.796
high/intermediate risk PCa receiving active treatment/follow-up;	0.789
advanced PCa	0.67
Disutility of biopsy (one-off)	0.035
Disutility due to AEs:	
acute sepsis	-0.43 (assumed duration 1 month)
erectile dysfunction [due to PCa treatment]	-0.10 [0.05; 0.15] (assumed duration 1 year)
urinary incontinence [due to PCa treatment]	-0.20 [0.1; 0.3] (assumed duration 1 year)
Both erectile dysfunction and urinary incontinence	-0.25 [0.125; 0.375] (assumed duration 1 year)

AE = adverse event, NR = not reported, PCa = prostate cancer, SD = standard deviation.

Source: Section C.4 Table 45; Section D.4 Table 60.

Adverse events

The mpMRI was not associated with any adverse events that were expected to substantially impact costs or benefits within the economic evaluation. Biopsy-related sepsis was considered to be a serious event with an associated cost and disutility. In the economic evaluation, the incidence of sepsis was assumed to be 1.2 per cent for all biopsy measures. In addition to biopsy-associated sepsis, the economic evaluation took into account common adverse events associated with prostate cancer treatments, erectile dysfunction and urinary incontinence, with disutilities of 0.1 and 0.2 per cent, respectively. For the probabilities of these treatment-related complications (0.415 for erectile dysfunction, 0.062 for urinary incontinence), an Australian quality of life study from the New South Wales Cancer Registry was used.

ECONOMIC EVALUATION

To quantify the trade-off between mpMRI costs and benefits, a cost-utility analysis was undertaken. The benefits of mpMRI in the model are associated with avoiding biopsies and overtreatment

associated with low to intermediate risk PCa in a proportion of the population. One model was developed to examine the cost-utility of mpMRI in both populations, allowing for the evaluation of the impact of mpMRI in Population 1 separately, Population 2 separately, or Population 1 and 2 together. A decision tree was used to model the diagnostic pathways, followed by a Markov model representing subsequent follow-up. Table 8 provides a summary of the economic evaluation.

Table 8 Summary of the economic evaluation

Perspective	MBS perspective
Comparator	TRUSGB/TPUSGB
Type of economic evaluation	Cost-utility analysis
Sources of evidence	Systematic review and meta-analysis of clinical trials [Section B] Targeted review for utility parameters [Section C] Expert opinion was elicited where no data were available
Time horizon	Lifetime time horizon (25 years) in the model base-case
Outcomes	QALYG
Methods used to generate results	Combined decision tree and Markov model using cohort expected value analysis
Health states	No prostate cancer Low to intermediate risk prostate cancer (insignificant cancer) Intermediate to high risk prostate cancer (significant cancer) Advanced prostate cancer Death
Cycle length	1 year
Discount rate	5% for costs and outcomes
Software packages used	TreeAge Pro 2015

MBS = Medical Benefit Schedule, TRUSGB = Trans-rectal ultrasound guided biopsy, TPUSGB = Trans-perineal ultrasound guided biopsy; QALYG = Quality-adjusted life-years gained.

Source: Section D.3 Table 51

Key structural assumptions of the model are:

- All patients enter the model at age 66, which is the mean age of PCa diagnosis in Australia. Over time patients that have entered the model will age, and their background mortality (obtained from ABS statistics) will change accordingly.
- All patients enter the model as men with suspected PCa (Population 1). Patients that are entering Population 2, men with low or intermediate risk PCa undergoing active surveillance, are a subset of what previously used to be Population 1.
- A cost associated with delayed diagnosis is applied for patients with false negative results. Delayed diagnosis was assumed not to impact PCa prognosis in the base-case.

- Patients with false positive results have the same prognosis as other patients without cancer, but were assumed to spend a year under “active surveillance” (as with low/intermediate risk prostate cancer patients).
- Patients may remain in any health state or progress, but may not regress.
- The introduction of mpMRI does not alter the rest of the clinical treatment algorithm, i.e. the types of biopsies used remains the same. For the base-case, a weighted average of the various types of biopsy is assumed (TRUSGB, 75%; and TPUSGB 25%). This assumption is made as MRIGB is currently not available on the MBS. The use of MRIGB was included in a sensitivity analysis. Accuracy of MRIGB was aligned with the assessment being conducted for MRIGB (CA 1424).
- Patients are managed according to the clinical algorithms presented in Section A.

Table 55 provides the test accuracy information used in the economic evaluation.

Table 9 Test accuracy of mpMRI and TRUSGB/TPUSGB

Description	Sensitivity, mean (95%CI)	Specificity, mean (95%CI)
mpMRI	73.4% (57%, 85%)	77.1% (63.5%, 86.7%)
TRUSGB/TPUSGB	81% (70%, 88%)	93.64% (89.4%, 96.3%)

CI = confidence interval, mpMRI = multiparametric MRI, MRIGB = magnetic resonance guided biopsy, TPUSGB = trans-perineal ultrasound guided biopsy, TRUSGB = trans-rectal ultrasound guided biopsy.

Source: Section D.4 Table 55

Prevalence of PCa in Population 1 was assumed to be 35 per cent for low concern patients and 50 per cent for intermediate to high concern patients, consistent with advice from the Applicant. The prevalence of progressed (significant) cancer in patients undergoing re-biopsy as part of active surveillance was assumed to be 15 per cent to reflect a proportion of approximately 8.8 per cent of men moving from active surveillance to radical treatment per year, under the current clinical algorithm (assuming sensitivity of re-biopsy is 0.81 and specificity is 0.94). Approximately 50 per cent of the patients were assumed to be of low-concern versus intermediate- to high-concern. The overall proportion of cancers that was assumed to be of low to intermediate risk (insignificant) as opposed to intermediate to high risk (significant) was assumed to be 90 per cent in the low-concern patients and 10 per cent in the intermediate- to high-concern patients.

Resource consumption was based on clinical guidelines and the treatment algorithms provided in the study Protocol. Unit costs were determined based on MBS fees for medical procedures. All costs were reported in Australian dollars from the year 2014. In case costs were obtained in previous years, they were inflated using the Health CPI. Table 59 provides an overview of all costs included in the economic evaluation.

Table 10 Costs in economic model

Cost description		Cost (\$)
Intervention costs		
Intervention: mpMRI		\$510.00
Comparator TRUSGB/TPUSGB (75/25)		\$604.05
Costs of PCa treatment		
Active surveillance	Year 1	\$5,367.47
	After year 1	\$981.54
Treatment of intermediate to high risk PCa	Year 1	\$11,640.89
	After year 1	\$2,313.13
Treatment of advanced PCa	Year 1	\$23,709.62
	After year 1	\$6,428.65
Delayed diagnosis		\$696.01
Cost of false positive		AS
AE due to mpMRI		\$0
AE due to TRUSGB		\$54.32
PSA test		\$31.75

AE = adverse event, AS = active surveillance, mpMRI = multiparametric MRI; PCa, prostate cancer; TPUSGB, trans-perineal ultrasound guided biopsy, TRUSGB, trans-rectal ultrasound guided biopsy.

Source: Section D.4 Table 59

The mpMRI can either be introduced in Population 1, or in Population 2, or in both. For each of these options, the table below provides the overall costs, outcomes, incremental costs and incremental outcomes as calculated for the intervention (mpMRI) and comparator (prostate biopsy) in the model, with the base-case assumptions. The table also provides the mean number of biopsies per patient in the model, for each of the strategies.

Table 11 Results of the economic evaluation

	Cost	Effectiveness (QALYs)	ICER	Biopsies per patient, mean (n)
Population 1 only				
Intervention mpMRI in Population 1, prostate biopsy in Population 2	\$12,990	7.40	Dominated	3.17
Comparator Prostate biopsy in Population 1 and 2.	\$12,635	7.45		3.61
Increment^b	\$355	-0.05		0.44 ^a biopsies avoided per patient
Population 2 only				
Intervention Prostate biopsy in Population 1, mpMRI in Population 2.	\$13,148	7.49	\$12,821	3.01
Comparator Prostate biopsy in Population 1 and 2.	\$12,635	7.45		3.61
Increment^b	\$513	0.04		0.60 ^a biopsies avoided per patient
Both populations				
Intervention mpMRI in Population 1 and 2.	\$13,490	7.43	Dominated	2.60
Comparator Prostate biopsy in Population 1 and 2.	\$12,635	7.45		3.61
Increment^b	\$855	-0.02		1.01 ^a biopsies avoided per patient
Gordon et al. (2016): Population 1				
Intervention Strategy 2: mpMRI±MRIGB	\$24,943	7.7	Dominated	1.14
Comparator Strategy 1: TRUSGB	\$24,203	7.82		1.44
Increment^b	\$740	-0.12		0.3 ^a biopsies avoided per patient
Intervention Strategy 3: mpMRI ± TRUS/TPUS or MRIGB	\$24,337	7.77	Dominated	1.10
Comparator Strategy 1: TRUSGB	\$24,203	7.82		1.44
Increment^b	\$134	-0.05		0.34 ^a biopsies avoided per patient

^a: Results reported are mean biopsies avoided per patient, i.e. favours intervention.

^b: Increment = intervention minus comparator.

ICER = Incremental Cost Effectiveness Ratio, QALYs = quality of life-years, MRIGB = magnetic resonance imaging guided biopsy, mpMRI = multiparametric MRI, TPUSGB, trans-perineal ultrasound guided biopsy, TRUSGB, trans-rectal ultrasound guided biopsy.

Source: Section D.3 Table 51

In Population 1, mpMRI is dominated (more costly, less effective) by the prostate biopsy. In Population 2, the incremental cost per quality of life year (QALY) gained by using mpMRI is \$12,821. For each of the strategies, mpMRI reduces the average number of biopsies needed per patient. This reduction is largest where mpMRI is introduced for both Population 1 and 2, resulting in an average of 1.01 biopsies avoided per patient. The introduction of mpMRI results in a higher number of

significant cancers diagnosed (613 versus 604 per 1,000 patients), while reducing the number of insignificant cancers diagnosed (625 versus 654 per 1,000 patients) at initial PCa diagnosis.

In Population 1, mpMRI is dominated by prostate biopsy in each of the scenarios, except when looking at a time horizon of 5 years only. With a 5 year time horizon, the incremental cost effectiveness ratio (ICER) of mpMRI over prostate biopsy is \$80,264 per QALY in Population 1. In Population 2, the ICER is most sensitivity to the use of MRIGB in addition to mpMRI in the intervention arm. In this sensitivity analysis, MRIGB was assumed to be used for all patients with PI-RADS 4-5, consistent with the proposed clinical algorithm in the Protocol 1397. This increases the ICER from \$12,821 to \$66,320 per QALY gained with mpMRI (see Table 12).

Table 12 Key drivers of the economic model

Description	Method/Value	Impact
Time horizon	5 and 10 years	High, favours intervention
Type of biopsies used	Use of MRIGB for patients with mpMRI PI-RADS 4-5	High, favours comparator

MRIGB = magnetic resonance imaging guided biopsy; mpMRI = multiparametric MRI; PI-RADS = Prostate Imaging Reporting and Data System.

ESTIMATED EXTENT OF USE AND FINANCIAL IMPLICATIONS

A combination of the market share approach (in Population 1 and 2) and the epidemiological approach (in Population 2) were used to estimate the financial implications of the introduction of mpMRI. The financial implications to the MBS resulting from the proposed listing of mpMRI, both in Population 1 and Population 2, are summarised in Table 13. The additional costs of mpMRI are partly offset by a reduction in prostate biopsies.

Table 13 Total costs to the MBS associated with mpMRI for prostate cancer.

	Yearly costs (Year 1 to Year 5)			Over 5 years (Total, Year 1-5)		
	Population 1	Population 2	Total	Population 1	Population 2	Total
mpMRI						
Number of services	13,276	6,873	20,149	66,380	34,365	100,745
Cost to MBS	\$6,770,760	\$3,505,230	\$10,275,990	\$33,853,800	\$17,526,150	\$51,379,950
Cost to patients	\$1,194,840	\$618,570	\$1,813,410	\$5,974,200	\$3,092,850	\$9,067,050
Total cost	\$7,965,600	\$4,123,800	\$12,089,400	\$39,828,000	\$20,619,000	\$60,447,000
Prostate biopsies avoided						
Number of services	-3,943	-1,718	-5,661	-19,715	-8,591	-28,306
Savings to MBS	-\$1,950,021	-\$849,771	-\$2,799,793	-\$9,750,107	-\$4,248,856	-\$13,998,964
Total cost to MBS	\$4,820,739	\$2,655,459	\$7,476,197	\$24,103,693	\$13,277,294	\$37,380,986

mpMRI = multiparametric MRI, MBS = Medical Benefits Schedule.
 Source: Section E.4 Table 66

ACRONYMS AND ABBREVIATIONS

ADT	Androgen Deprivation Therapy
AE	Adverse Event
AIHW	Australian Institute of Health and Welfare
AMSTAR	A Measurement Tool to Assess Systematic Reviews
AR-DRG	Australian Refined Diagnostic Related Groups
ARTG	Australian Register of Therapeutic Goods
AS	Active Surveillance
BPE	Benign Prostate Enlargement
BRCA	Breast Cancer
bx	Biopsy
CA	Contracted Assessment
CAD	Canadian Dollars
CEA	Cost Effectiveness Analysis
CI	Confidence Interval
CPI	Consumer Price Index
CRPC	Castrate Resistant Prostate Cancer
CUA	Cost Utility Analysis
DAP	Decision Analytic Protocol
DCE	Dynamic Contrast Enhancement
DPMQ	Dispense Price for Maximum Quantity
DRE	Digital Rectal Examination
DWI	Diffusion Weighted Imaging
EBRT	External Beam Radiotherapy
EUR	Euros
GBP	Great British Pound

HESP	Health Expert Standing Panel
HRQoL	Health-Related Quality Of Life
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
IHR	Intermediate to High Risk
IQR	Interquartile Range
LR	Low Risk
LY	Life years
MBS	Medicare Benefits Schedule
MCRPCa	Metastatic Castrate Resistant Prostate Cancer
MD	Mean Difference
ml	Millilitre
mpMRI	Multiparametric MRI
MRGB	Magnetic Resonance Guided Biopsy
MRI	Magnetic Resonance Imaging
MRIGB	MRI Guided Biopsy
MSAC	Medical Services Advisory Committee
NA	Not Applicable
ng	Nanogram
NHCDC	National Hospital Cost Data Collection
NHMRC	National Health and Medical Research Council
NHS	United Kingdom, National Health System
NR	Not Reported
PASC	Protocol Advisory Sub-Committee
PBS	Pharmaceutical Benefits Scheme
PCa	Prostate Cancer
PCA3	Prostate Cancer Gene 3

PHI	Prostate Health Index
PICO	Patient Intervention Comparator Outcome
PI-RADS	Prostate Imaging Reporting and Data System
PSA	Prostate Specific Antigen
QALY	Quality Adjusted Life-Years
QALYG	Quality Adjusted Life-Years Gained
RANZCR	Royal Australian New Zealand College of Radiologists
RP	Radical Prostatectomy
SD	Standard Deviation
T2W	T2 Weighted
TGA	Therapeutic Goods Administration
TPUSGB	Trans-perineal Ultrasound Guided Biopsy
TRUSGB	Trans-rectal Ultrasound Guided Biopsy
TURP	Transurethral Resection Of The Prostate
USD	United States dollars
USGB	Ultrasound Guided Biopsy
UTI	Urinary Tract Infection

SECTION A

CONTEXT

This contracted assessment of multiparametric MRI (mpMRI) scans for diagnosis of prostate cancer (PCa) is intended for the Medical Services Advisory Committee (MSAC). MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Schedule (MBS) in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

ASERNIP-S of the Royal Australasian College of Surgeons has been commissioned by the Australian Government Department of Health to conduct a systematic literature review and economic evaluation of mpMRI prostate diagnostic scans for diagnosis of PCa. This assessment has been undertaken in order to inform MSAC's decision-making regarding whether the proposed medical service should be publicly funded. It should be noted that a related service, MRI-guided prostate biopsy is also being assessed. It is currently being assessed as CA 1424.

The proposed use of mpMRI prostate diagnostic scans for diagnosis of PCa in Australian clinical practice was outlined in a Protocol that was presented to, and accepted by, the Protocol Advisory Sub-Committee (PASC) (DoH 2016a). The Protocol was released for public comment on 30-31 June 2015.

A1 ITEMS IN THE AGREED PROTOCOL

This contracted assessment of mpMRI prostate diagnostic scans for diagnosis of PCa addresses all of the Population, Intervention, Comparator, Outcomes (PICO) elements that were pre-specified in the Protocol ratified by PASC. **PROPOSED MEDICAL SERVICE**

A2.1 Description of intervention

The proposed service for Application 1397 is mpMRI for cancer detection in patients with suspicion of PCa and disease monitoring in patients with known disease who are on active surveillance (AS) programs.

Magnetic resonance imaging (MRI) uses a magnet and radio-waves to produce images of soft tissues. MRI utilises strong, uniform magnetic fields to investigate the anatomy, perfusion, tissue characterisation and function of different organs and systems within the human body. When hydrogen protons present in human cells are exposed to this magnetic field, they align along its rotational axis in a uniform plane. In order to generate an image, a sequence of smaller magnetic pulses is targeted towards the area of interest, exciting the protons, which then release

radiofrequency signals upon relaxation. These signals are converted into an image, which represents the concentration of hydrogen protons in different tissue, making MRI particularly useful for imaging soft tissues with a high concentration of water.

In mpMRI, three pulse sequences are used: T2 weighted (T2W), diffusion weighted imaging (DWI) and dynamic-contrast enhanced (DCE). These are combined and analysed together.

The magnetic field strength within conventional MRI scanners are either 1.0T (Teslas), 1.5T or 3T, with higher strength fields producing higher resolution images. The use of higher strength fields allows for images with a higher spatial resolution and more clearly defined anatomical structures, but increases the chance imaging artefacts that can obscure the image. Both 1.5 and 3.0 Tesla MRI scanners are available in Australia; either one may be used to carry out multiparametric scans (HealthPACT 2015). However, although the new generation 1.5 Tesla MRI scanners may be adequate for mpMRI, the older generation machines are not, as they are unable to acquire the DWI (DoH 2016a). DWI is a measure of the tissue density of a lesion in the prostate and is a vital tool in diagnosis of cancer within the prostate, as greater than 95 per cent of prostate cancers are denser than normal prostate tissue.

During imaging patients are required to lie in the MRI machine, moving as little as possible. Prostate imaging can be conducted with or without an endorectal coil in Australia; the Applicant advises that an endorectal coil is rarely used in New Zealand (DoH 2016a).

mpMRI is scored using the Prostate Imaging Reporting and Data System (PI-RADS) v2 scoring system, which uses a five-point assessment scale to indicate the likelihood that mpMRI findings correlate with the presence of clinically significant cancer at a particular location in the prostate. The PI-RADS v2 assessment categories are defined with the following scores:

1. Very low (clinically significant PCa is highly unlikely to be present)
2. Low (clinically significant PCa is unlikely to be present)
3. Intermediate (the presence of clinically PCa disease is equivocal)
4. High (clinically significant PCa is likely to be present)
5. Very high (clinically significant PCa is highly likely to be present)

The assessment category for each lesion is determined by scoring DWI, T2 and DCE MRI sequences. The DWI and T2 sequences are scored using a five-point scale, whereas a two-point scale (positive or negative) is used for scoring DCE (Barentsz et al. 2016).

Biopsy to confirm the presence of PCa is the current practice for both patient populations. As defined in the proposed clinical algorithm, mpMRI would be used before biopsy to identify patients who do not have clinically significant cancer and will not require biopsy (Figure 1).

A3 PROPOSAL FOR PUBLIC FUNDING

The proposed MBS item descriptor is summarised in Table 14.

Table 14 Proposed MBS item descriptor

Category 5 – Diagnostic Imaging Services
<p>MBS [item number]</p> <p>Multiparametric Magnetic Resonance Imaging (mpMRI) performed under the professional supervision of an eligible provider at an eligible location where the patient is referred by an urologist, radiation oncologist, or medical oncologist and where:</p> <p>a) a standardised image acquisition protocol involving T2 weighted imaging, Diffusion Weighted Imaging, and Dynamic Contrast Enhancement (unless contraindicated) is used; and</p> <p>b) the man is suspected of having prostate cancer on the basis of a high or concerning PSA.</p> <p>Scan of the prostate for:</p> <p>– detection of cancer (R)(Contrast)</p> <p>Fee: [Applicant advises that current fee charged is \$600]</p> <p>[Relevant explanatory notes]</p>
<p>MBS [item number]</p> <p>Multiparametric Magnetic Resonance Imaging (mpMRI) performed under the professional supervision of an eligible provider at an eligible location where the patient is referred by an urologist, radiation oncologist, or medical oncologist and where:</p> <p>a) a standardised image acquisition protocol involving T2 weighted imaging, Diffusion Weighted Imaging, and Dynamic Contrast Enhancement (unless contraindicated) is used; and</p> <p>b) the man has an existing diagnosis of low or intermediate risk prostate cancer and is undertaking Active Surveillance.</p> <p>Scan of the prostate for:</p> <p>– assessment of cancer (R)(Contrast)</p> <p>Fee: [Applicant advises that current fee charged is \$600]</p> <p>[Relevant explanatory notes]</p>

A4 PROPOSED POPULATION

While the cause(s) of PCa are not yet completely understood, age, family history, lifestyle, ethnic background, and environmental factors may play a role. Amongst Australian men PCa is the fourth leading cause of death after heart disease, lung cancer, and cerebrovascular diseases. In 2013, there were nearly 3,112 deaths from PCa, and the age-standardised mortality rate for PCa was 27 per 100,000 males (AIHW 2016). In 2012, there were 20,065 new cases of PCa diagnosed in Australia. The age-standardised incidence rate was 163 cases per 100,000 males (AIHW 2016).

An MBS listing is requested for multiparametric MRI (mpMRI) scans of the prostate for two populations:

1. men who are suspected of having PCa on the basis of a high or concerning PSA; and
2. men diagnosed with low or intermediate risk PCa undertaking AS.

A4.1 UTILISATION

A4.1.1 MEN WITH SUSPECTED PROSTATE CANCER

A method for estimating the number of eligible men is to assume that all men who currently receive a prostate biopsy would have an mpMRI scan if the service was listed on the MBS.

The estimate used in this analysis to determine the number of eligible patients is based on the assumption that all patients who received a biopsy would have opted for an mpMRI had this service been available. Between July 2014 and June 2015, there were 20,149 services claimed on the MBS for ultrasound-guided prostate biopsy (MBS item 37219). From this, there would potentially be 13,554¹ mpMRI services for men with suspected PCa. This is likely an underestimation of utilisation, as men who refused a prostate biopsy may opt to undergo mpMRI scanning if the proposed items are listed.

Applicant advice informs that 50 per cent of men with suspected PCa are high-concern and 50 per cent are low-concern. Approximately, 30 to 40 per cent of low-concern patients will have PCa and 5-10 per cent of low-concern patients (13-33% of low-concern patients with cancer) will have clinically significant cancer. In high-concern patients, 50 per cent will have cancer and 90 per cent of these will have clinically significant cancer (Applicant 2016).

A4.1.2 MEN DIAGNOSED WITH LOW OR INTERMEDIATE RISK PROSTATE CANCER UNDERTAKING ACTIVE SURVEILLANCE

Active surveillance (sometimes called watchful waiting) involves deferred treatment along with disease monitoring, usually with PSA testing, DRE, and sometimes repeat biopsy (Eberhardt et al. 2013).

Data from the Victorian Prostate Cancer Registry indicates that 15.3 per cent of patients newly diagnosed with PCa are opting to manage their disease with AS (Weerakoon et al. 2015). Applying this to the prevalence data, there may be approximately 13,190 men undergoing AS for PCa. It should be noted that as AS is an emerging strategy this number may underestimate future utilisation of AS as a treatment for PCa.

Under the proposed protocol for mpMRI in AS (see Figure 4), men would have a scheduled mpMRI scan at 12 months and then every three years thereafter. Men may also have an mpMRI scan at any

¹ Of the 20,149 biopsies performed annually, it is estimated that 6,595 are performed for active surveillance (AS patients are assumed to receive an average of one biopsy every two years). Subtracting these patients from the total leaves the estimated 13,554 biopsies performed for patients in Population 1.

other time due to concerns about clinical or PSA changes. Assuming that, on average, men on AS will have an mpMRI scan once every two years, this would equate to 6,595 mpMRI services per year.

Applicant advice informs that 14 per cent of men on AS are high-concern and 86 per cent are low-concern. Approximately 30-35 per cent will experience an upgrade to their disease status (Applicant 2016).

A4.2 ADMINISTRATION, DOSE, FREQUENCY OF ADMINISTRATION, DURATION OF TREATMENT

An mpMRI scan of the prostate is an image acquisition protocol using T2W, DWI and DCE, as outlined above in A2.1. The Applicant has advised that the approximate duration of a 3T mpMRI scan of the prostate is 35 minutes, and the duration of a 1.5T scan is approximately 45 minutes.

Following negative mpMRI, Population 1 patients would remain under observation with PSA repeated at six month periods. Active surveillance patients would be scanned at 12 months, and then every three years.

All mpMRI scans of the prostate are performed in a radiology department. The proposed service would require specialist referral from an urologist, radiation oncologist, or medical oncologist.

Current legislative requirements stipulate that Medicare eligible MRI items must be reported on by a trained and credentialed specialist in diagnostic radiology who satisfies the Chief Executive Medicare that the specialist radiologist is a participant in the Royal Australian and New Zealand College of Radiologist's (RANZCR) Quality and Accreditation Program (Australian Government 2013).

A5 COMPARATOR DETAILS

Currently in Australia, the signs of PCa are detected with a prostate-specific antigen test (PSA test) and/or a digital rectal examination (DRE).

The PSA test quantifies the amount of PSA in the blood stream. The PSA may be present in the blood stream for many reasons – including infection or trauma to the prostate, benign prostatic enlargement (BPE), and PCa. Consequently, the PSA test has a low specificity of approximately 25 to 30 per cent (DoH 2016a). Overall, an elevated level of PSA may be indicative of an elevated risk of PCa, but this has not been confirmed (Barentsz et al. 2012; HealthPACT 2015).

The DRE test involves inserting a finger into the rectum to palpate the prostate; swellings, hardenings or lumps may be signs of PCa. While DRE has a low sensitivity, its positive predictive value is high – hard lumps detected by DRE are likely to be PCa (DoH 2016a).

As reported above, PSA and DRE tests are not diagnostic; a diagnosis of PCa is made on the basis of biopsy results. Biopsy, while not the direct comparator, is the current clinical practice for this patient

group with concerning PSA/DRE. Biopsy has therefore been addressed in this assessment in the comparator and reference test sections.

During a biopsy, a needle is inserted trans-rectally or trans-perineally into the prostate and a set of random samples of tissue (using between 12-36 needles) are taken from the prostate (Applicant 2016). The samples are then analysed under a microscope, to see if cancer cells are present (AIHW 2013; Siddiqui et al. 2015). Cancers of the prostate are graded using the Gleason system: Gleason score of 6 or less is considered low risk, a Gleason score of 7 is considered intermediate risk, and a score of 8 or above is considered to be high risk (HealthPACT 2015). Another risk stratification measure in use is the TNM Classification of Malignant Tumours (TNM), where T describes the size of the tumour, N describes the affected lymph nodes, and M describes the metastases (Cancer Council Australia 2015).

For men who are suspected of having PCa on the basis of a high or concerning PSA, the comparators are:

1. PSA/DRE + clinical judgement and US-guided trans-rectal or trans-perineal guided biopsy (TRUSGB or TPUSGB)
2. PSA/DRE + clinical judgement alone, for patients who elect not to undergo TRUSGB or TPUSGB

For men diagnosed with low or intermediate risk PCa undertaking AS, the comparator is the current AS protocol with routine re-biopsies.

Current MBS item for ultrasound scans of the prostate are included in Table 15.

Table 15 Current MBS item descriptors for scans of the prostate

Subgroup 4 - Urological
<p>MBS item 55600 Prostate, bladder base and urethra, ultrasound scan of, if performed: (a) personally by a medical practitioner (not being the medical practitioner who assessed the patient as specified in paragraph (c)) using one or more transducer probes that: (i) have a nominal frequency of 7 to 7.5 MHz or a nominal frequency range that includes frequencies of 7 to 7.5 MHz; and (ii) can obtain both axial and sagittal scans in 2 planes at right angles; and (b) after a digital rectal examination of the prostate by that medical practitioner; and (c) on a patient who has been assessed by a specialist in urology, radiation oncology or medical oncology, a consultant physician in medical oncology, who has: (i) examined the patient in the 60 days before the scan; and (ii) recommended the scan for the management of the patient's current prostatic disease (R) (K) (See para DIQ of explanatory notes to this Category) Fee: \$109.10 Benefit: 75% = \$81.85 85% = \$92.75</p>
<p>MBS item 55601 PROSTATE, bladder base and urethra, ultrasound scan of, where performed: (a) personally by a medical practitioner (not being the medical practitioner who assessed the patient as specified in (c))</p>

<p>using a transducer probe or probes that:</p> <p>(i) have a nominal frequency of 7 to 7.5 megahertz or a nominal frequency range which includes frequencies of 7 to 7.5 megahertz; and</p> <p>(ii) can obtain both axial and sagittal scans in 2 planes at right angles; and</p> <p>(b) following a digital rectal examination of the prostate by that medical practitioner; and</p> <p>(c) on a patient who has been assessed by a specialist in urology, radiation oncology or medical oncology or a consultant physician in medical oncology who has:</p> <p>(i) examined the patient in the 60 days prior to the scan; and</p> <p>(ii) recommended the scan for the management of the patient's current prostatic disease (R) (NK)</p> <p><i>(See para DIQ of explanatory notes to this Category)</i></p> <p>Fee: \$54.55 Benefit: 75% = \$40.95 85% = \$46.40</p>
<p>MBS item 55603</p> <p>PROSTATE, bladder base and urethra, ultrasound scan of, where performed:</p> <p>(a) personally by a medical practitioner who undertook the assessment referred to in (c) using a transducer probe or probes that:</p> <p>(i) have a nominal frequency of 7 to 7.5 megahertz or a nominal frequency range which includes frequencies of 7 to 7.5 megahertz; and</p> <p>(ii) can obtain both axial and sagittal scans in 2 planes at right angles; and</p> <p>(b) following a digital rectal examination of the prostate by that medical practitioner; and</p> <p>(c) on a patient who has been assessed by a specialist in urology, radiation oncology or medical oncology or a consultant physician in medical oncology who has:</p> <p>(i) examined the patient in the 60 days prior to the scan; and</p> <p>(ii) recommended the scan for the management of the patient's current prostatic disease (R) (K)</p> <p><i>(See para DIQ of explanatory notes to this Category)</i></p> <p>Fee: \$109.10 Benefit: 75% = \$81.85 85% = \$92.75</p>
<p>MBS item 55604</p> <p>PROSTATE, bladder base and urethra, ultrasound scan of, where performed:</p> <p>(a) personally by a medical practitioner who undertook the assessment referred to in (c) using a transducer probe or probes that:</p> <p>(i) have a nominal frequency of 7 to 7.5 megahertz or a nominal frequency range which includes frequencies of 7 to 7.5 megahertz; and</p> <p>(ii) can obtain both axial and sagittal scans in 2 planes at right angles; and</p> <p>(b) following a digital rectal examination of the prostate by that medical practitioner; and</p> <p>(c) on a patient who has been assessed by a specialist in urology, radiation oncology or medical oncology or a consultant physician in medical oncology who has:</p> <p>(i) examined the patient in the 60 days prior to the scan; and</p> <p>(ii) recommended the scan for the management of the patient's current prostatic disease (R) (NK)</p> <p><i>(See para DIQ of explanatory notes to this Category)</i></p> <p>Fee: \$54.55 Benefit: 75% = \$40.95 85% = \$46.40</p>

The current MBS item for the biopsy portion of ultrasound-guided biopsy of the prostate is summarised below Table 16.

Table 16 Relevant MBS item descriptor for item 37219

Group T8 – Surgical Operations
MBS item 37219 PROSTATE, needle biopsy of, using prostatic ultrasound techniques and obtaining 1 or more prostatic specimens, being a service associated with a service to which item 55600 or 55603 applies Multiple services rule. (Anaes.) (Assist.) Fee: \$280.85 Benefit: 75% = \$210.65 85% = \$238.75

A6 CLINICAL MANAGEMENT ALGORITHM(S)

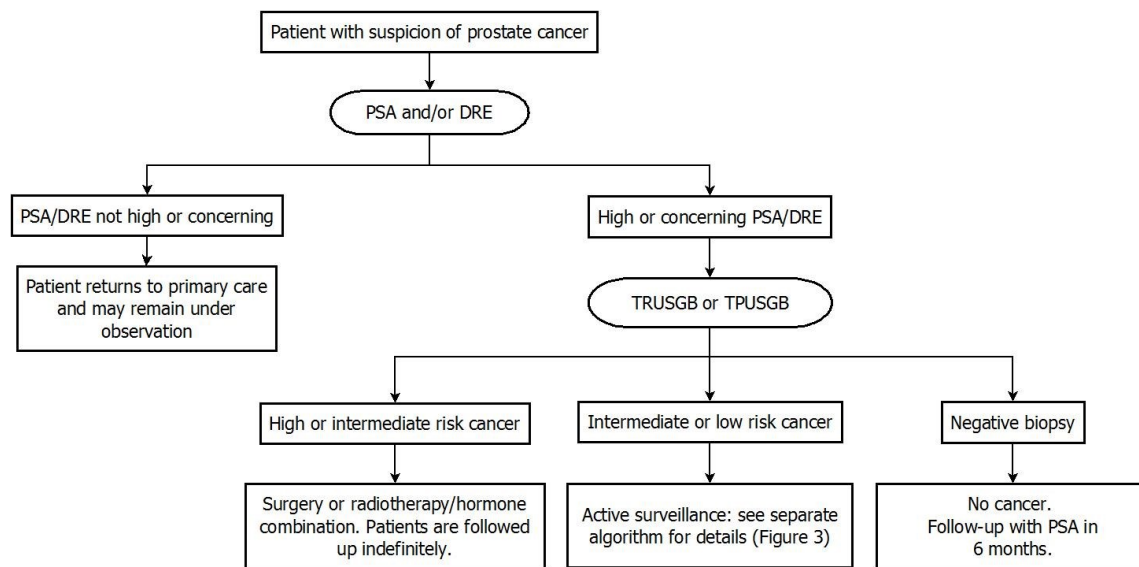
A6.1 POPULATION 1

Currently, the signs of PCa are detected with a PSA and/or a DRE test. Criteria for suspected PCa, for the purposes of this contracted assessment, are defined as:

- PSA greater than 3ng/ml (or lower level if less than 50 years of age (Barentsz et al. 2012); or
- Positive family history (includes breast cancer (BRCA) gene mutation); or
- Free/total PSA ratio less than 25 per cent; or
- Positive DRE.

The PSA and DRE tests are not diagnostic; diagnosis is obtained via either TRUSGB or TPUSGB. The current clinical management algorithm is outlined in Figure 1. Patients who receive a negative biopsy result will remain under observation and have a follow-up PSA test after six months. Patients with a biopsy result indicating intermediate or low risk cancer will be offered AS, which is detailed in Figure 3. Patients with a biopsy result indicating high risk or intermediate risk cancer will be offered surgery or a radiotherapy/hormone therapy combination.

Figure 1 Current clinical management algorithm without the proposed intervention



PSA = prostate-specific antigen test, DRE = digital rectal examination, TRUSGB = trans-rectal ultrasound guided biopsy, TPUSGB = trans-perineal ultrasound guided biopsy.

Under the proposed clinical management algorithm, patients with suspected PCa would be imaged using mpMRI. The proposed clinical management algorithm is outlined in Figure 2.

Patients with PI-RADS scores 1, 2, or 3 with low-concern, will return to primary care and may remain under observation. These patients will avoid a biopsy under the proposed algorithm. Patients with PI-RADS score of 1, 2, or 3 with very high- or intermediate-concern will have a systematic biopsy under both the current and proposed algorithms. Patients with PI-RADS scores 4 or 5, regardless of clinical concern, will have a magnetic resonance guided biopsy (MRIGB) of the lesion (either MRI/US fusion, in-gantry or cognitive targeting methods) in place of a systematic biopsy under current management. High- or intermediate-concern is defined as:

- Positive family history/ BRCA gene mutation; or
- Free/total PSA ratio less than 12 per cent; or
- PSA density greater than 0.15.

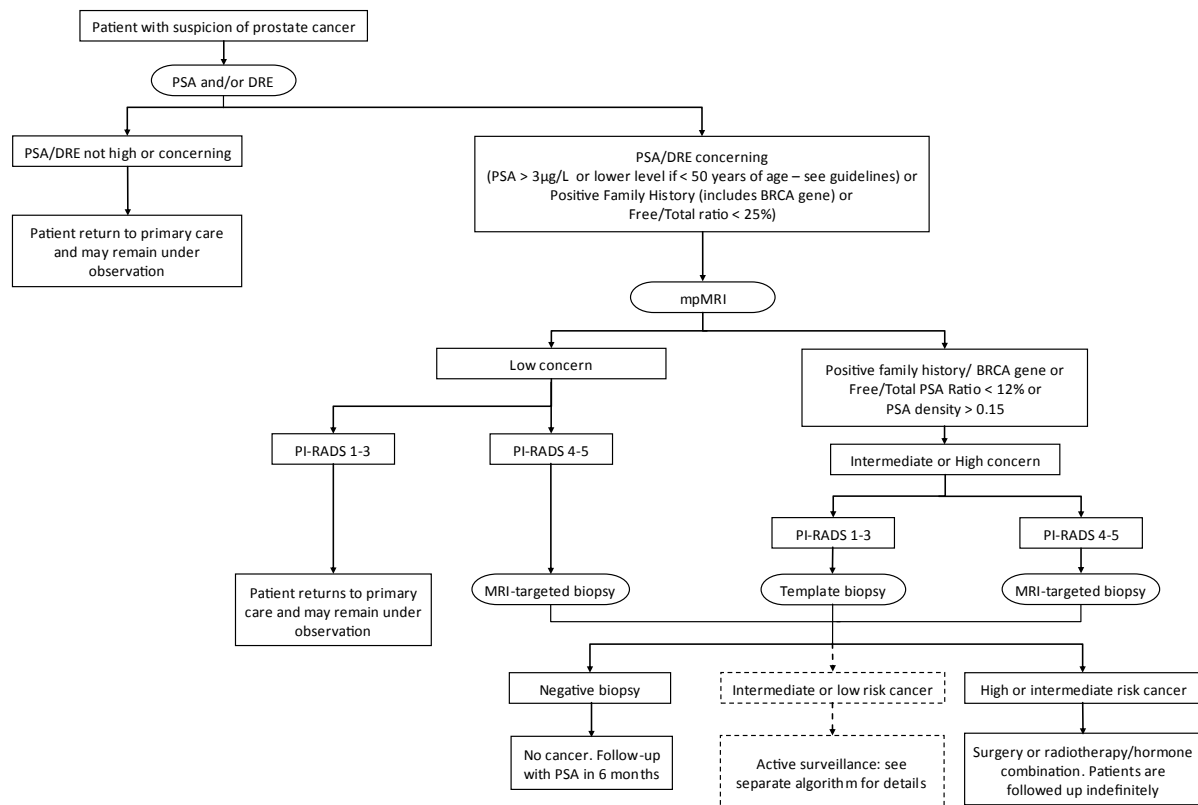
Low-concern is defined as patients who have suspected PCa but do not meet the criteria for high- or intermediate-concern.

Based on the results of the biopsy, patients would either:

- Return to primary care under observation, with a follow-up PSA test after six months; or
- Begin AS of their disease; or
- Have surgery or a radiotherapy/hormone therapy combination for their cancer.

The impact of the change in management from TRUSGB to MRIGB is the subject of CA 1424.

Figure 2 Proposed clinical management algorithm for diagnostic mpMRI



PSA = prostate-specific antigen test, DRE = digital rectal examination, PI-RADS = Prostate Imaging-Reporting and Data System, MR = magnetic resonance, mpMRI = multiparametric magnetic resonance imaging, MRIGB = magnetic resonance guided biopsy, US = ultrasound.

Note: Indications of increased cancer concern may include patient’s age, positive family history, abnormal DRE, PSA doubling time <2 years, PSA density >0.15, free/total PSA ratio <25%, Prostate Health Index >25, known BRCA1 or BRCA2 gene mutation.

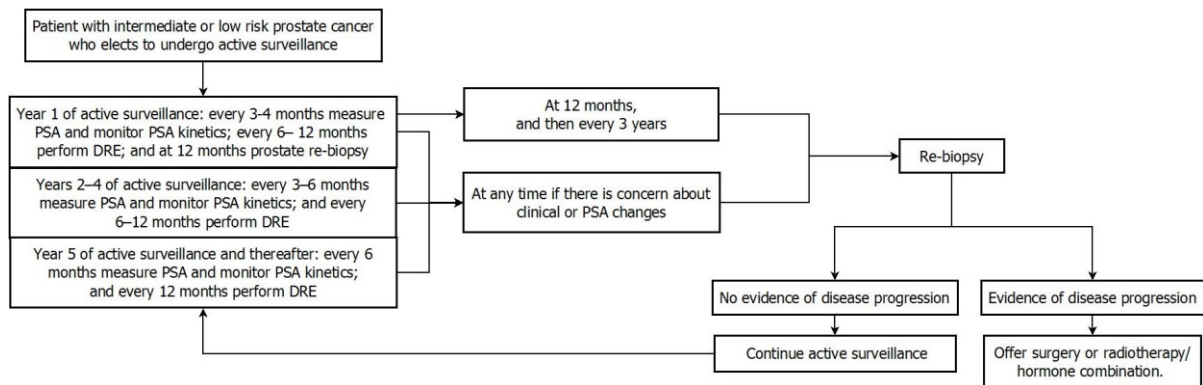
A6.2 POPULATION 2

Men who have a diagnosis of intermediate or low risk cancer may choose to participate in AS. During AS, men undergo scheduled testing (PSA, PSA kinetics and DRE) over a period of five years or more. Those on AS also have a scheduled prostate biopsy at 12 months and then every three years thereafter. At any point in time, if there is concern about clinical or PSA/DRE changes, men may opt to have an additional prostate biopsy. Based on the results of these biopsies, men will either continue on AS or be offered surgery or a radiotherapy/hormone therapy combination for their cancer. AS protocol detailed in Figure 3 is based on the Applicant’s advice and the recent NICE guidelines (Applicant 2016; NICE 2014).

If the proposed mpMRI service is added to the AS protocol it would be used as an additional test prior to prostate biopsy. Men who are due for their scheduled biopsy and men who have concern about clinical or PSA/DRE changes would first have an mpMRI scan. The criteria for concern are the same as for clinical scenario 1. Men with PI-RADS scores 1, 2, and 3 with low-concern would return to AS and avoid biopsy under the proposed algorithm. Men with high- or intermediate- concern and men with low-concern and a PI-RADS score of 4 or 5 would continue with a re-biopsy. Patients with a

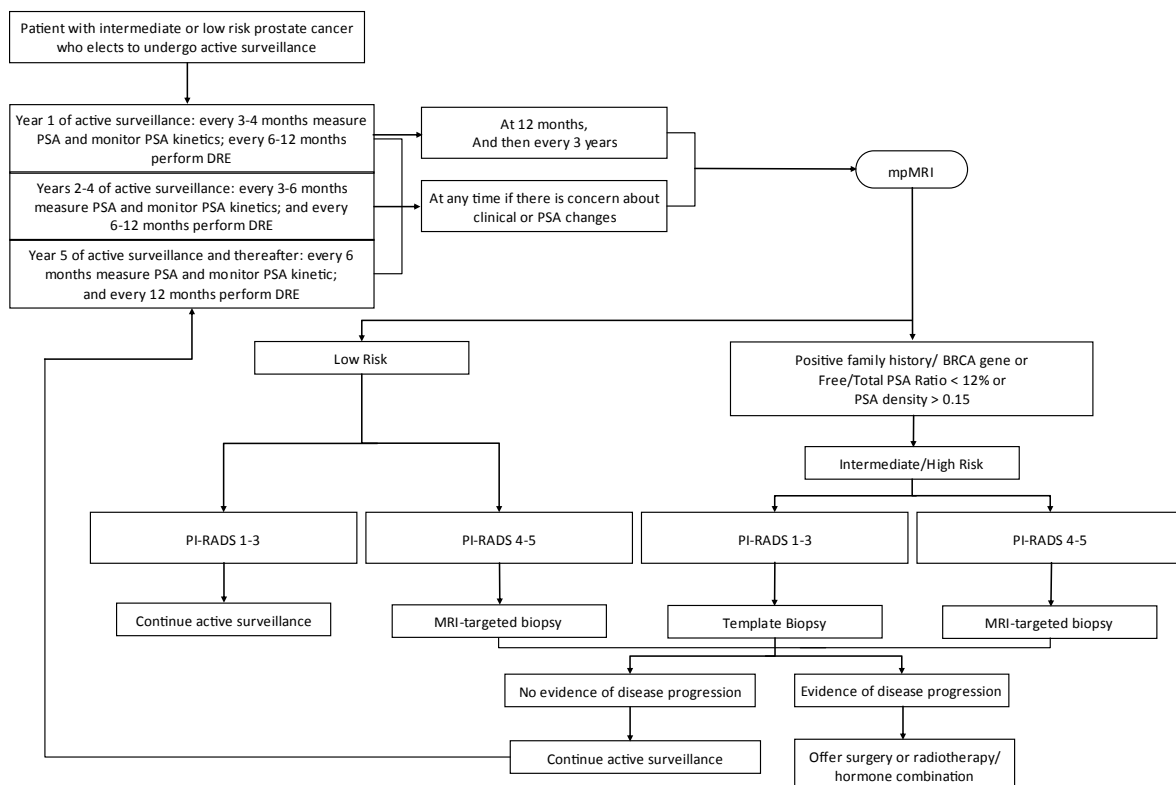
PI-RADS score of 4 or 5 would have an MRIGB biopsy, while patients with a PI-RADS score of 1-3 (high- or intermediate-concern) would have a systematic biopsy. Based on the results of these biopsies, men would either continue on AS or be offered surgery or a radiotherapy/hormone therapy combination for their cancer. The details of the proposed protocol for AS are presented in Figure 4. The impact of the change in management from TRUSGB to MRIGB is the subject of CA 1424.

Figure 3 Current protocol for active surveillance without the proposed intervention



PSA = prostate-specific antigen test, DRE = digital rectal examination.

Figure 4 Proposed protocol for active surveillance with mpMRI



PSA = prostate-specific antigen test, DRE = digital rectal examination PI-RADS = Prostate Imaging-Reporting and Data System, MR = magnetic resonance, mpMRI = multiparametric magnetic resonance imaging, US = ultrasound.

A7 KEY DIFFERENCES IN THE PROPOSED MEDICAL SERVICE AND THE MAIN COMPARATOR

A7.1 Patient indications

Indications for both mpMRI scan of prostate and biopsy of prostate are men with suspicious findings on PSA and/or DRE tests with suspected PCa, or men diagnosed with low or intermediate risk PCa undertaking AS.

A7.2 Contraindications

mpMRI

Contraindications for mpMRI include claustrophobia; having internal ferromagnetic objects such as implants; hypotension; and, using diuretics or vasodilators.

Biopsy

Contraindications for TRUSGB of the prostate include an acute painful perianal disorder (anal fissure), a haemorrhagic diathesis (unusual susceptibility to bleed), and diabetes mellitus which carries a risk of infection (Simsir et al. 2010; Suzuki et al. 2009); as well as recent urogenital infection before biopsy (Roberts et al. 2002). Patients should be discouraged from taking aspirin or non-steroidal anti-inflammatory drugs for at least 10 days before the procedure, but recent use of these agents should not be considered an absolute contraindication for prostate biopsy (Rodriguez and Terris 1998). No contraindications for TPUSGB of the prostate were identified.

A7.3 Likelihood and severity of adverse events

The risk profiles for mpMRI and biopsy (any type) differ due to the nature of the techniques as mpMRI is non-invasive imaging technique and biopsy is an invasive procedure.

mpMRI

MRI is an established technique, the likelihood of adverse events is very low, the severity of adverse events is generally low, and MRI is considered safe for most patients. The most relevant safety issues associated with mpMRI are the risks associated with internal ferromagnetic objects, and heat stress which is only seen as risky in patients with hypertension and patients taking diuretics or vasodilators (Schenck 2001a; Schenck 2001b). There is a potential risk of contact burns if patient positioning is inappropriate (Shellock FG 2001). Claustrophobia may prevent some patients from undergoing MRI scans (Thorpe et al. 2008). There are limited adverse events associated with gadolinium-based contrast agents (Bluemke et al. 2005). While it is recognised that there are also potential risks associated with the use of strong magnetic fields, these are unlikely to occur and are associated with higher field strengths than those used in clinical practice.

Biopsy

Different biopsy techniques may have different risk profiles. For any trans-rectal biopsy, the main risk is infection due to the insertion of needles through the rectum which is non-sterile. At its most severe, infection may cause sepsis and death although this is very rare. Risk of infection is reduced by antibiotic prophylaxis and pre biopsy workup including enema (Kapoor et al. 1998). Other complications of prostate biopsy include bleeding (haematuria, hematospermia, and hematochezia), urinary tract infection (UTI), and urinary obstruction. In trans-perineal biopsy risk of infection is lower due to the sterile nature of the perineum, where the needles are inserted. Trans-perineal also results in less rectal bleeding. It can; however, lead to perineal haematoma, but this is mild and uncommon (Rodriguez and Terris 1998).

A8 CLINICAL CLAIM

The clinical claim is that mpMRI scans of the prostate have better diagnostic accuracy (hence, more effective) and are safer than the current approach (DoH 2016a). In the event that claims of superior efficacy and safety are supported by the literature, cost-utility analysis would be appropriate (Table 17).

Table 17 Classification of an intervention for determination of economic evaluation to be presented

		Comparative effectiveness versus comparator				
		Superior		Non-inferior	Inferior	
Comparative safety versus comparator	Superior	CEA/CUA		CEA/CUA	Net clinical benefit	CEA/CUA
					Neutral benefit	CEA/CUA*
					Net harms	None^
	Non-inferior	CEA/CUA		CEA/CUA*	None^	
	Inferior	Net clinical benefit	CEA/CUA	None^	None^	
		Neutral benefit	CEA/CUA*			
Net harms		None^				

* May be reduced to cost-minimisation analysis. Cost-minimisation analysis should only be presented when the proposed service has been indisputably demonstrated to be no worse than its main comparator(s) in terms of both effectiveness and safety, so the difference between the service and the appropriate comparator can be reduced to a comparison of costs. In most cases, there will be some uncertainty around such a conclusion (i.e. the conclusion is often not indisputable). Therefore, when an assessment concludes that an intervention was no worse than a comparator, an assessment of the uncertainty around this conclusion should be provided by presentation of cost-effectiveness and/or cost-utility analyses.

^ No economic evaluation needs to be presented; MSAC is unlikely to recommend government subsidy of this intervention.

CEA = cost-effectiveness analysis, CUA = cost-utility analysis.

A9 SUMMARY OF THE PICO

The guiding framework of a PICO Confirmation, or Protocol, is recommended by MSAC for each assessment. The Protocol describes current clinical practice and reflects the likely future practice with the proposed medical service.

The Population, Prior tests, Investigation/Index test, Comparator and Outcomes (PPICO) that were pre-specified to guide the systematic literature review of the direct effectiveness and safety of the index and comparator interventions, are presented in Box 1 to Box 3.

Box 1 Criteria for identifying and selecting studies to determine the safety of mpMRI of the prostate in men with suspicion of prostate cancer or on active surveillance

Selection criteria	Description
Population	Men with suspected PCa or men diagnosed with low or intermediate risk PCa undertaking active surveillance
Intervention	mpMRI scan of prostate
Comparators	No limit on comparator
Outcomes	Critical for decision making: adverse events following mpMRI
Systematic review question	What are the safety outcomes associated with mpMRI of the prostate in patients with suspicion of PCa?

PCa = prostate cancer, CA = contracted assessment, mpMRI = multiparametric MRI, MRI = magnetic resonance imaging.

Box 2 Criteria for identifying and selecting studies to determine the safety of prostate biopsy in patients with suspicion of prostate cancer or on active surveillance

Selection criteria	Description
Population	Men with suspected PCa or men diagnosed with low or intermediate risk PCa undertaking active surveillance
Intervention	Clinical judgement and sometimes biopsy of prostate (trans-rectal, trans-perineal, MRI-guided)
Comparators	Not specified or no limit of comparator
Outcomes	Critical for decision making: mortality and adverse events, complications of biopsy
Systematic review question	What are the safety outcomes associated with biopsy of the prostate (TRUSGB, MRIGB or TPUSGB) in patients with suspicion of PCa?

PCa = prostate cancer, mpMRI = multiparametric MRI, MRI = magnetic resonance imaging, TRUSGB = trans-rectal ultrasound guided biopsy, TPUSGB = trans-perineal ultrasound guided biopsy, MRIGB = magnetic resonance imaging guided biopsy.

Box 3 Criteria for identifying and selecting studies to determine the direct effectiveness of mpMRI in patients with suspicion of prostate cancer or on active surveillance

Selection criteria	Description
Population	Men with suspected PCa or men diagnosed with low or intermediate risk PCa undertaking active surveillance
Prior tests	PSA, DRE, genetic testing, family history
Intervention	mpMRI scan of prostate
Comparator	TRUSGB or TPUSGB
Outcomes	Critical for decision making: Patient health outcomes, survival, PCa specific mortality, change in incontinence, change in impotence
Systematic review question	What is the direct effectiveness of mpMRI compared to TRUSGB or TPUSGB in men with suspected PCa or men diagnosed with low or intermediate risk PCa undertaking active surveillance?

PCa = prostate cancer, PSA = prostate-specific antigen, DRE = digital rectal examination, mpMRI = multiparametric MRI, MRI = magnetic resonance imaging, TRUSGB = trans-rectal ultrasound guided biopsy, TPUSGB = trans-perineal ultrasound guided biopsy.

The Population (and in some cases prior tests), Investigation/Index test, Comparator and Outcomes (PICO) that were pre-specified to guide the systematic literature review for the linked evidence assessment of mpMRI scans of the prostate, are presented in Box 4 to Box 7.

Box 4 Criteria for identifying and selecting studies to determine the accuracy of mpMRI scan of prostate in patients with suspicion of prostate cancer or on active surveillance

Selection criteria	Description
Population	Men with suspected PCa or men diagnosed with low or intermediate risk PCa undertaking active surveillance
Prior tests	DRE or PSA
Index test	mpMRI scan of prostate
Comparator	Clinical judgement and sometimes biopsy of prostate (trans-rectal, trans-perineal, MRI-guided)
Outcomes	Sensitivity, specificity, PPV, NPV, changes in the biopsy rate, changes in the rate of men diagnosed with low risk cancer, change in the rates of surgery, quality of life, satisfaction, time from diagnosis to treatment
Systematic review question	What is the diagnostic accuracy of Multiparametric MRI of the prostate in men with suspected PCa or men diagnosed with low or intermediate risk PCa undertaking active surveillance?

PCa = prostate cancer, PSA = prostate-specific antigen, DRE = digital rectal examination, MRI = magnetic resonance imaging, PPV = positive predictive value, NPV = negative predictive value.

Box 5 Criteria for identifying and selecting studies to determine the reliability of PI-RADS in patients with suspicion of prostate cancer or on active surveillance

Selection criteria	Description
Population	Men with suspected PCa or men diagnosed with low or intermediate risk PCa undertaking active surveillance
Intervention	PI-RADS scoring system for evaluating PCa with mpMRI with biopsy as reference standard
Comparator	Not specified
Outcomes	Critical for decision making: Inter-rater reliability/reproducibility / kappa Important, but not critical for decision making: Low importance for decision making:
Systematic review question	How reliable is PI-RADS for evaluating PCa in men with suspected cancer or men diagnosed with low or intermediate risk PCa undertaking active surveillance?

PCa = prostate cancer, PI-RADS = Prostate Imaging Reporting and Data System, mpMRI = multiparametric MRI, MRI = magnetic resonance imaging.

Box 6 Criteria for identifying and selecting studies to determine the accuracy of prostate biopsy in patients with suspicion of prostate cancer or on active surveillance

Selection criteria	Description
Population	Men with suspected PCa or men diagnosed with low or intermediate risk PCa undertaking active surveillance
Prior tests	DRE or PSA
Index test	Biopsy of prostate
Study type	Systematic review
Comparator	Not specified
Outcomes	As above
Systematic review question	What is the diagnostic accuracy of prostate biopsy (TRUSGB, TPUSGB or MRIGB) in men with suspected PCa or men diagnosed with low or intermediate risk PCa undertaking active surveillance? (As the diagnostic accuracy of prostate biopsy has been established and is the current practice, a systematic review was sought to answer the question.)

PCa = prostate cancer, DRE = digital rectal examination, PSA = prostate-specific antigen, TRUSGB = trans-rectal ultrasound guided biopsy, TPUSGB = trans-perineal ultrasound guided biopsy, MRIGB = magnetic resonance imaging guided biopsy, MRI = magnetic resonance imaging.

Box 7 **Criteria for identifying and selecting studies to determine the patient outcomes subsequent to mpMRI scan of prostate in patients with suspicion of prostate cancer or on active surveillance**

Selection criteria	Description
Population	Men with a false negative, missed diagnosis, delayed treatment, untreated, inappropriate treatment or wrong diagnosis for PCa
Intervention	NA
Comparator	Not specified
Outcomes	Impact of deferred treatment, inappropriate treatment, or misdiagnosis, survival, time from diagnosis to treatment
Systematic review question	What is the impact of deferred treatment, inappropriate treatment, and misdiagnosis in men with PCa?

PCa = prostate cancer.

A10 **CONSUMER IMPACT STATEMENT**

In conducting this assessment, ASERNIP-S requested from the Department of Health any available impact statements used in the preparation of the PASC ratified protocol. None was provided; as such, consumer impact has not been addressed in this assessment.

SECTION B

CLINICAL EVALUATION

- There was insufficient direct evidence to assess the effectiveness of mpMRI in Population 1 or 2 (Subsection B1).
- A linked evidence approach was taken – this is described in Subsection B2.

B1 DIRECT EVIDENCE

B1.1 LITERATURE SOURCES AND SEARCH STRATEGIES: DIRECT EVIDENCE (POPULATIONS 1 AND 2)

The medical literature was searched on 20 May 2016 to identify relevant studies. The search was not date limited. Searches were conducted of the databases and sources described in Appendix B. Search terms are described in Table 18.

Table 18 PubMed search strategy

Element of clinical question	Search terms
Population	(prostate) OR prostate[MeSH Terms]
Intervention	(((((multiparametric magnetic resonance imaging) OR multiparametric MRI) OR multiparametric-MRI) OR MP-MRI) OR MP MRI) OR MPMRI) OR MP-magnetic resonance imaging) OR MP magnetic resonance imaging)) OR ((((((diffusion weighted) OR DW) OR diffusion-weighted)) AND dynamic) AND T1) AND T2) AND (((MRI) OR magnetic resonance imaging) OR magnetic resonance imaging[MeSH Terms]))
Comparator (if applicable)	NA
Outcomes (if applicable)	NA
Limits	None

This search strategy was adapted for the Ovid EMBASE, Cochrane databases.

MRI = magnetic resonance imaging, MP-MRI = multiparametric magnetic resonance imaging, NA = not applicable, DW = diffusion weighted.

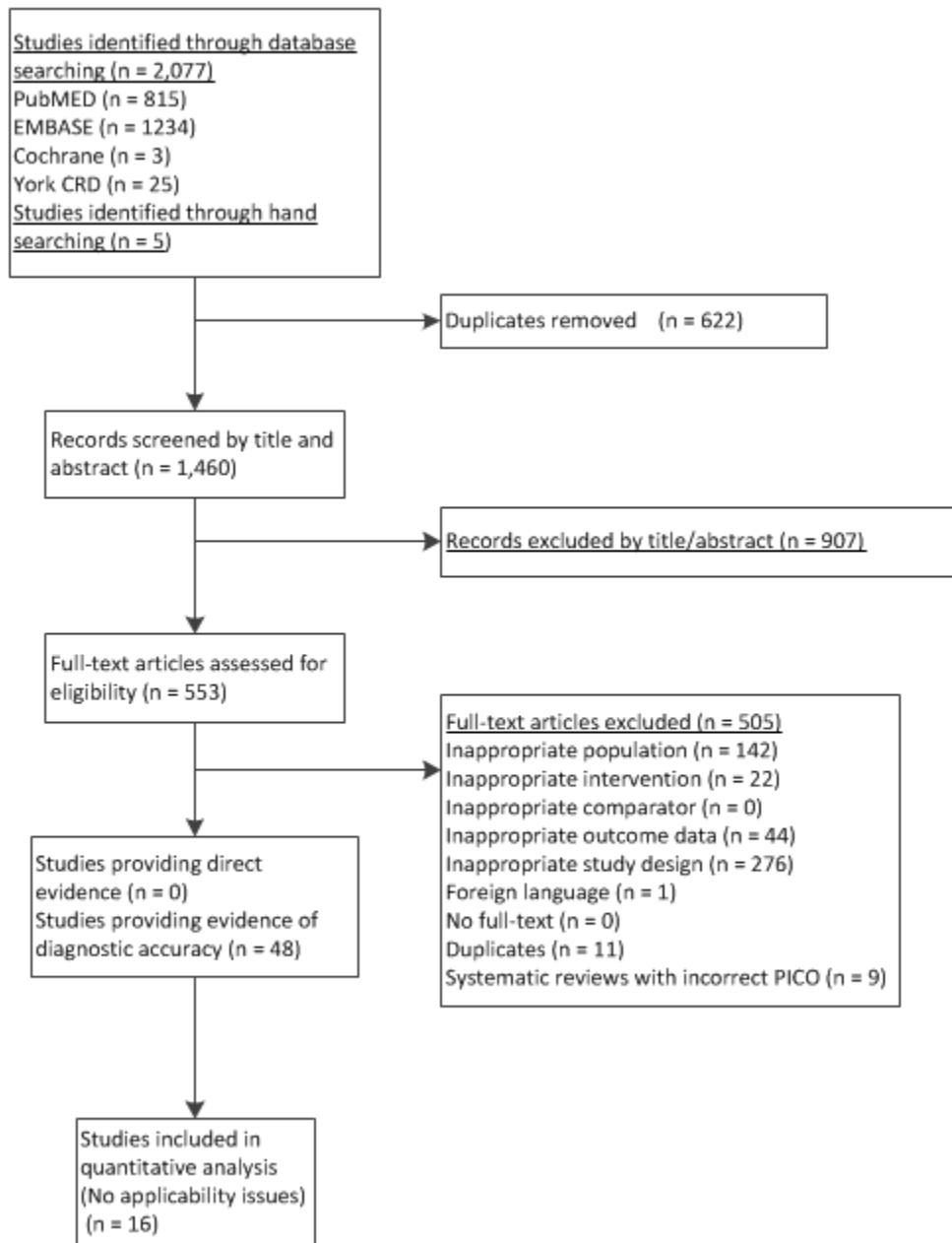
B1.2 RESULTS OF LITERATURE SEARCH: DIRECT EVIDENCE (POPULATIONS 1 AND 2)

The PRISMA flowchart (Liberati et al. 2009) in Figure 5 provides a graphic depiction of the results of the literature search and the application of the study selection criteria (listed in Box 1, 2 and 3, Subsection A9).

Studies were screened by title and abstract by a single reviewer with a random sample receiving independent assessment by a second reviewer. Full-text review to select included studies was performed independently by two reviewers. Disagreements regarding study selection were resolved by a third independent reviewer.

All studies that met the inclusion criteria are listed in Appendix C. Studies that could not be retrieved or that met the inclusion criteria but contained insufficient or inadequate data for inclusion are listed as excluded studies in Appendix E.

Figure 5 Summary of the process used to identify and select studies for the assessment



No studies were identified that provided direct evidence of the safety and effectiveness of mpMRI in either Population 1 or Population 2.

The linked evidence approach used for this assessment is described in Section B2.

B2 LINKED EVIDENCE APPROACH

B2.1 BASIS FOR LINKED EVIDENCE

No direct evidence on the effectiveness of mpMRI was identified therefore a linked evidence approach was undertaken for this assessment.

A linked evidence approach is justified as there is evidence available to inform the diagnostic performance, clinical utility and relative safety of mpMRI in patient populations consistent with those outlined in the Protocol.

B2.2 STEPS FOR LINKED ANALYSIS

The following steps were undertaken to complete the linked analysis:

- Consideration of the diagnostic performance of mpMRI (Section B3);
- Consideration of the clinical utility of mpMRI in terms of impact of positive versus negative test results on patient management, the contribution and clinical importance of false negatives versus false positives and direct impact of each therapeutic model service option on health outcomes (Section B5);
- Considerations of the impact of use of mpMRI for disease monitoring (Section B6); and
- Consideration of the relative safety of performing mpMRI, both immediate safety issues of directly performing the test and 'flow on' safety issues that arise as a result of conducting the investigative service (Section B7).

Conclusions informed by the linked analysis are reported in Section B8.

B3 DIAGNOSTIC PERFORMANCE

An MBS listing is requested for mpMRI scans of the prostate for two populations:

1. men who are suspected of having PCa on the basis of a high or concerning PSA (Population 1); and
2. men diagnosed with low or intermediate risk PCa undertaking AS (Population 2).

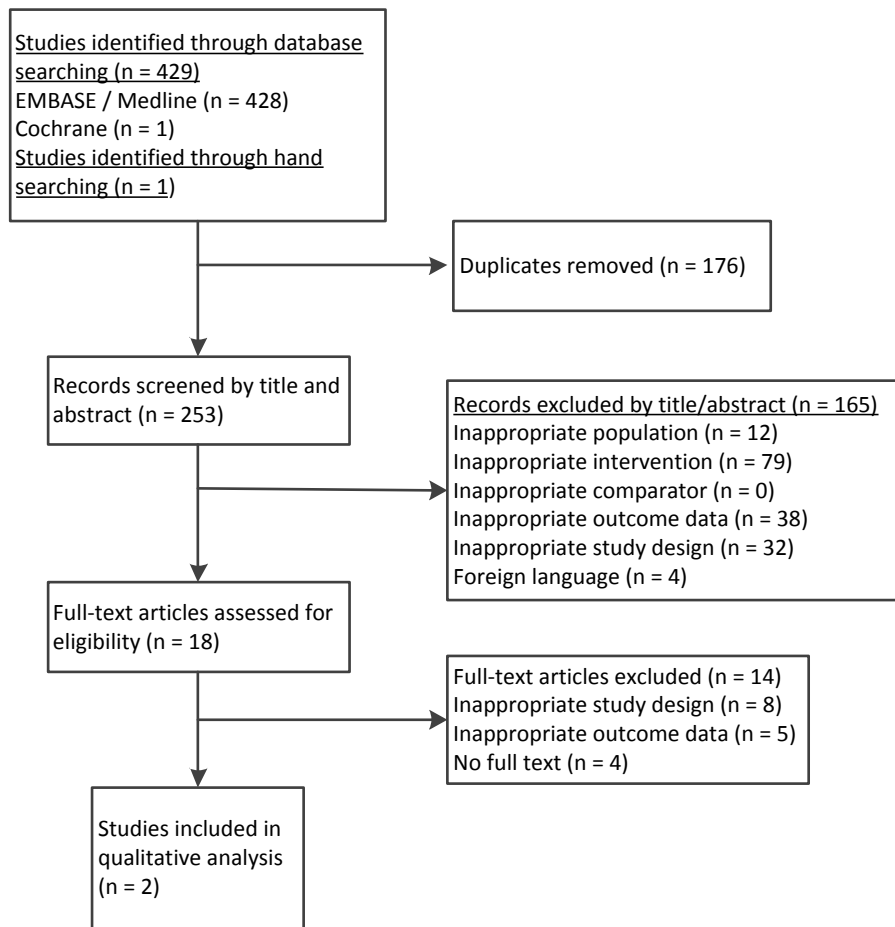
The diagnostic performance of mpMRI in Population 1 is discussed in Subsection B3, the use of mpMRI to monitor patients on AS is reported in Subsection B6.

B3.1 REFERENCE STANDARD

The reference standard for PCa is histology of pathological samples. In diagnostic cases such samples are best taken by biopsy. In Australia prostate tissue samples are obtained by trans-rectal biopsy in 84 per cent of cases and trans-perineal biopsy in seven per cent of cases. The remaining prostate samples are obtained following transurethral resection of the prostate or transurethral resection of a bladder tumour (Sampurno et al. 2015). Prostate biopsy can be guided by US, MRI or US/MRI fusion.

It is acknowledged that biopsy is not a perfect reference standard. A systematic review of the literature was performed to identify any systematic reviews that could inform the diagnostic accuracy of TRUSGB or TPUSGB. The search criteria included systematic reviews reporting the diagnostic accuracy of TRUSGB or TPUSGB (Box 6, Subsection A9). The PRISMA flowchart shown in Figure 6 provides a graphic depiction of the results of the literature search (Liberati et al. 2009). The search resulted in two systematic reviews presenting diagnostic accuracy data for trans-rectal and trans-perineal ultrasound guided prostate biopsy.

Figure 6 Summary of the process used to identify and select studies to inform the diagnostic accuracy of biopsy



Two systematic reviews were identified that assessed the diagnostic accuracy of biopsy. Both reviews were judged to have a low risk of bias (Table 81, Appendix F) using the AMSTAR assessment tool (Shea et al. 2007). The main limitation of both systematic reviews being a failure to report a list of excluded studies.

One systematic review was identified that compared TRUSGB with MRIGB) (Schoots et al. 2015). Schoots et al. (2015) included 16 studies with a total of 1,926 patients. TRUSGB was compared to MRIGB in a concordance analysis as no study reported use of a surgical specimen reference standard. TRUSGB was found to have a sensitivity of 0.81 (95% CI [0.70, 0.88]) in the detection of PCa, while MRIGB was found to have a sensitivity of 0.85 (95% CI [0.80, 0.89]). The difference in sensitivity between the two biopsy techniques was not statistically significant.

The second systematic review (Shen et al. 2012) compared TRUSGB with TPUSGB. Results for different biopsy techniques (sextant, extensive and saturation) were reported separately. In two case-control studies conducting sextant biopsy, there was no significant difference between TRUSGB (38.31%) and TPUSGB (40.67%) in the cancer detection rate (Relative difference [RD], -0.02, 95% CI [-0.08, -0.03], $p=0.34$). In three randomised controlled trials (RCTs) and one case-control study

comparing extensive prostate biopsies, there was no significant difference between TRUSGB (33.00%) and TPUSGB (33.73%) in the cancer detection rate (RD, -0.01, 95% CI [-0.05, 0.04], $p=0.81$). One case-control study on saturation biopsy found no statistically significant difference in the PCa detection rate between TRUSGB and TPUSGB (41.4% and 25.7%, respectively, $p=0.3$).

For the purposes of this Assessment, it is assumed that TRUSGB, TPUSGB and MRIGB have equivalent diagnostic accuracy.

B3.2 LITERATURE SOURCES AND SEARCH STRATEGIES: DIAGNOSTIC ACCURACY (POPULATION 1)

The search strategy used to identify diagnostic accuracy studies is described in Subsection B1.1.

B3.2.1 RESULTS OF LITERATURE SEARCH: DIAGNOSTIC ACCURACY (POPULATION 1)

In the PRISMA flowchart at Figure 5 Subsection B1.1, Liberati et al. (2009) provides a graphic depiction of the results of the literature search and the application of the study selection criteria as listed in Box 4 (Subsection A9).

An overview of the diagnostic accuracy studies are shown in Table 19 (Population 1). A full profile of each included study is given in Appendix C. Data were extracted into *a priori* designed extraction templates by a single researcher and data extraction was checked by a second researcher. Those studies which technically met the inclusion criteria, but which were not included in the results section or meta-analyses, are listed in Appendix E.

A total of 33 primary studies, including 6,606 patients, that assessed the diagnostic accuracy of mpMRI against prostate biopsy in patients with a concerning PSA or DRE result were identified (Table 19) (Abd-Alazeez et al. 2014b; Baldisserotto et al. 2016; Baur et al. 2016; Busetto et al. 2013; De Visschere et al. 2016; Dikaios et al. 2014; Ferda et al. 2013; Girometti et al. 2012; Haffner et al. 2011; Hauth et al. 2015; Itatani et al. 2014; Jambor et al. 2014; Komai et al. 2013; Lamb et al. 2015; Lista et al. 2015; Panebianco et al. 2015; Pepe et al. 2014a; Petrillo et al. 2014; Pokorny et al. 2014; Porpiglia et al. 2014; Renard-Penna et al. 2016; Rosenkrantz et al. 2013b; Rouse et al. 2011; Tamada et al. 2011; Tanimoto et al. 2007; Thompson et al. 2014; Thompson et al. 2016; Tonttila et al. 2016; Vilanova et al. 2011; Wang et al. 2015; Washino et al. 2016; Wysock et al. 2016; Zhao et al. 2016). A profile of each included study is provided in Appendix C.

To avoid any threshold effects from influencing the results, studies were pooled according to whether a PI-RADS threshold of ≥ 4 was used (or calculable) to signify a positive result. Studies where only data using PI-RADS ≥ 3 threshold was available were grouped; similarly studies where the threshold was not reported or where the PI-RADS system was not used were also reported separately. Only studies using a PI-RADS threshold of ≥ 4 , consistent with the proposed usage of

mpMRI detailed in the Protocol have been used to inform the diagnostic performance, clinical utility and economic analyses. Results on the diagnostic accuracy of studies not using a PI-RADS ≥ 4 threshold are reported in Appendix G.

Including only studies using the PI-RADS ≥ 4 threshold, 11 studies including 2,116 patients were identified for Population 1 (Abd-Alazeez et al. 2014b; Baldisserotto et al. 2016; Baur et al. 2016; Dikaios et al. 2014; Jambor et al. 2014; Lista et al. 2015; Pokorny et al. 2014; Thompson et al. 2014; Thompson et al. 2016; Wang et al. 2015; Zhao et al. 2016).

Table 19 Key features of the included evidence comparing mpMRI against prostate biopsy in Population 1

Trial/Study	n	Level of evidence ^a	Risk of bias ^b	Key outcome(s) ^c	Result used in meta-analysis ^d
Abd-Alazeez et al. (2014)	54	III-2	Unclear	TP, TN, FP, FN	Not used, per-patient analysis not available
Baldisserotto et al. (2016)	54	III-2	High	TP, TN, FP, FN	Used
Baur et al. (2016)	45	III-2	High	TP, TN, FP, FN	Used
Busetto et al. (2013)	163	III-2	High	TP, TN, FP, FN	Not used – other threshold
De Visschere et al. (2016)	830	III-2	Unclear	TP, TN, FP, FN	Not used – other threshold
Dikaios et al. (2015)	85	III-2	High	TP, TN, FP, FN	Used
Ferda et al. (2013)	191	III-2	High	TP, TN, FP, FN	Not used – other threshold
Girometti et al. (2012)	26	III-2	High	TP, TN, FP, FN	Not used – other threshold
Haffner et al. (2011)	555	III-2	High	TP, TN, FP, FN	Not used – PI-RADS ≥ 3
Hauth et al. (2015)	94	III-2	High	TP, TN, FP, FN	Not used – PI-RADS ≥ 3
Itatani et al. (2014)	193	III-2	High	TN, FN	Not used – bivariate data not available
Jambor et al. (2014)	55	III-2	Unclear	TP, TN, FP, FN	Used
Komai et al. (2013)	324	III-2	High	TP, TN, FP, FN	Not used – PI-RADS ≥ 3
Lamb et al. (2015)	173	III-2	Unclear	TP, TN, FP, FN	Not used – other threshold
Lista et al. (2015)	150	III-2	Unclear	TP, TN, FP, FN	Used
Panebianco et al. (2015)	570	III-2	Unclear	TP, TN, FP, FN	Not used – PI-RADS ≥ 3
Pepe et al. (2014)	168	III-2	High	TP, TN, FP, FN	Not used – other threshold
Petrillo et al. 2013	136	II	Unclear	TP, TN, FP, FN	Not used – other threshold

Trial/Study	n	Level of evidence ^a	Risk of bias ^b	Key outcome(s) ^c	Result used in meta-analysis ^d
Pokorny et al. (2014)	226	II	High	TP, TN, FP, FN	Used
Porpiglia et al. (2014)	170	III-1	Unclear	TP, TN, FP, FN	Not used – other threshold
Renard-Penna et al. (2016)	78	III-2	Unclear	TN, FN	Not used – bivariate data not available
Rosenkrantz et al. (2013)	42	III-2	High	TP, TN, FP, FN	Not used – other threshold
Rouse et al. (2011)	114	III-2	High	TP, TN, FP, FN	Not used – PI-RADS ≥ 3
Tamada et al. (2011)	50	III-2	High	TP, TN, FP, FN	Not used – other threshold
Tanimoto et al. (2007)	83	III-2	High	TP, TN, FP, FN	Not used – other threshold
Thompson et al. (2014)	150	III-2	High	TP, TN, FP, FN	Used
Thompson et al. (2016)	344	III-2	Unclear	TP, TN, FP, FN	Used
Tonttila et al. (2016)	113	III-2	High	TP, TN, FP, FN	Not used – other threshold
Vilanova et al. (2011)	70	II	Low	TP, TN, FP, FN	Not used, per-patient analysis not available
Wang et al. (2015)	586	III-2	High	TP, TN, FP, FN	Used
Washino et al. (2016)	288	III-1	High	TP, TN, FP, FN	Not used – PI-RADS ≥ 3
Wysock et al. (2016)	54	III-2	Unclear	TN, FN	Not used only – bivariate data not available
Zhao et al. (2016)	372	III-2	High	TP, TN, FP, FN	Used

^a: I=systematic review of level II studies; II=a study of test accuracy with an independent, blinded comparison with a valid reference standard, among consecutive patients with a defined clinical presentation; III-1=at study of test accuracy with an independent blinded comparison with a valid reference standard, among non-consecutive persons with a defined clinical presentation; III-2=a comparison with reference standard that does not meet the criteria for level II and III-1 evidence; III-3=diagnostic case-control study; IV=study of diagnostic yield (no reference standard).

^b: If any domain in the QUADAS-II assessment of risk of bias was rated as high then the overall assessment was high. If no domain was judged to have a high risk of bias but any domain was rated unclear then the overall assessment was rated as unclear. An overall rating of low was only given to studies where every domain had a low risk of bias. The breakdown of risk of bias by domain is provided in Subsection B3.3.

^c: Only TP, TN, FP and FN data were extracted from the primary studies, where sensitivity and specificity data only were reported then this was used to calculate TP, TN, FP and FN data.

^d Only studies that reported bivariate diagnostic accuracy outcomes on a per-patient basis that used a PI-RADS ≥ 4 threshold were included. Some studies used a ≥ 3 PI-RADS threshold, these are presented separately in Appendix G. Other threshold refers to studies that did not report what threshold they used or that used a system other than PI-RADS to analyse the mpMRI images. These are also presented in Appendix G.

TP = true positive, FP = false positives, TN = true negative, FN = false negative, PI-RADS = Prostate Imaging Reporting and Data System.

APPRAISAL OF THE EVIDENCE

Appraisal of the evidence was conducted in 4 stages:

Stage 1: Appraisal of the risk of bias within individual studies (or systematic reviews) included in the review (Subsections B3.3, B5.2.3 & B6.3).

Stage 2: Appraisal of the precision, size of effect and clinical importance of the results reported in the evidence base as they relate to the pre-specified primary outcomes for this assessment (Subsections B3.6, B5.2.6 & B6.6).

Stage 3: Rating the overall quality of the evidence per outcome, across studies, based on the study limitations (risk of bias), imprecision, inconsistency of results, indirectness of evidence, and the likelihood of publication bias (Evidence profile tables, Appendix D).

Stage 4: Integration of this evidence (across outcomes) to form conclusions about the net clinical benefit of the test and associated interventions in the context of Australian clinical practice (Section B.8).

B3.3 RISK OF BIAS ASSESSMENT: DIAGNOSTIC ACCURACY (POPULATION 1)

Risk of bias of the identified diagnostic accuracy studies was determined using a modified version of the QUADAS-2 quality appraisal tool (Whiting et al. 2011). The QUADAS-2 quality appraisal tool, with triggering questions and the criteria used to apply the tool is outlined in Table 80 while the results from the quality appraisal are summarised in Table 82 (Appendix F). Quality appraisal was performed by one researcher and checked by a second. Any disagreement was resolved by consensus agreement with a third researcher.

Risk of bias was assessed in four domains: patient selection, index test, reference standard, and flow and timing. No study was excluded due to an inappropriate risk of bias.

In the 'patient selection' domain 20 studies were found to have a low risk of bias. One study (Ferda et al. 2013) was judged to have a high risk of bias due to the exclusion of some, but not all, patients with a negative MRI from biopsy. Twelve studies were assessed to have an unclear risk of bias in this domain. This was largely due to a failure to report whether patient enrolment was consecutive (12 studies) and/or a failure to report exclusion criteria (four studies).

In the 'index test' domain 22 studies were found to have a low risk of bias. Two studies were judged to have a high risk of bias for failing to determine the threshold for a positive test *a priori* (Baldisserotto et al. 2016; Washino et al. 2016). Nine studies were assessed to have an unclear risk of bias due to a failure to report whether the mpMRI results were interpreted without knowledge of

the biopsy results (seven studies) and/or whether the threshold for a positive result was determined *a priori* (four studies).

In the 'reference standard' domain risk of bias was assessed to be low in six studies, high in 13 studies due to a lack of blinding to the results of the index test and unclear in 14 studies due to inexplicit reporting of whether the result of the reference test were interpreted without knowledge of the index test. All studies used a reference standard that was likely to classify to the condition correctly; pathology from biopsy specimens was used in all studies.

In the 'flow and timing' domain nine studies were assessed as having a low risk of bias. Eight studies were assessed to have a high risk. This was primarily due to the reference standard being performed more than three months after the mpMRI images were obtained in some or all included patients. In addition, Washino et al. (2016) only included patients with high risk disease in the reported results. Pokorny et al. (2014) had three patients withdraw from the study who were therefore not included in the analysis. Ferda et al. (2013) did not include all patients in the analysis as discussed above. Sixteen studies did not report the timing of the reference standard in relation to the index test and were therefore judged to have an unclear risk of bias in this domain. Results of the QUADAS-2 appraisal are presented in Table 82, Appendix F.

There was no applicability issue identified relating to patient selection or the choice of reference standard in any of the included studies. Twenty-two studies were assessed as having applicability issues relating to the index test. None of these studies used a PI-RADS ≥ 4 as the threshold for a positive result. This applicability issue was judged to be serious as the threshold used in a diagnostic accuracy study will have a large impact on the sensitivity and specificity results. Due to this, studies with an applicability issue were not included in the meta-analysis of results; however, results from these studies are reported separately in Appendix G.

B3.4 CHARACTERISTICS OF THE EVIDENCE BASE: DIAGNOSTIC ACCURACY (POPULATION 1)

Appendix C contains the tabulated details of the entire cohort of individual studies included in the evidence base. Only studies without applicability issues are discussed in detail in this section of the report. These studies are referred to as 'key studies' (Baldisserotto et al. 2016; Baur et al. 2016; Dikaios et al. 2014; Jambor et al. 2014; Lista et al. 2015; Pokorny et al. 2014; Thompson et al. 2014; Thompson et al. 2016; Wang et al. 2015; Zhao et al. 2016). While Abd-Alazeez et al. (2014) did not have any applicability issues, per-patient results were not reported and therefore this study was not included as a key study.

Selected characteristics of the key studies for Population 1 are presented in Table 20.

Overall patient characteristics in the key studies were judged to be consistent with the proposed population (Population 1) in the Protocol. Only studies that included patients with a suspicion of PCA were included. Studies which limited inclusion to patients with known disease were excluded from this assessment due to the potential for verification bias and applicability issues. All key studies included patients on the basis of concerning PSA and/or DRE results; however, only two studies reported the PSA cut-off they used as an inclusion criterion. Both Jambor et al. (2014) and Lista et al. (2015) included patients with a PSA greater than 4ng/ml. The mean PSA in the key studies ranged from 8.4 to 15.0ng/ml while the median PSA ranged from 5.2-10ng/ml, these are in line with median PSA levels reported by the Victorian Prostate Cancer Registry (median PSA 7.8ng/ml and the South Australian Prostate Cancer Clinical Outcomes Collaborative (median PSA 6.5ng/ml) (Kinnear et al. 2016; Ruseckaite et al. 2016; SA Prostate Cancer Clinical Outcomes Collaborative 2014). Patients in the key studies had a mean age ranging from 62.4-70.0 years or a median age ranging from 62.9-66 years. This is consistent with the mean age at diagnosis for men in the Victorian Registry of 66 years and the South Australian Registry of 67 years (Kinnear et al. 2016; Ruseckaite et al. 2016; SA Prostate Cancer Clinical Outcomes Collaborative 2014).

The included studies did not report results separately for patients with high-concern (defined as a positive family history/BRCA gene mutation, a free/Total PSA Ratio <12% or a PSA density >0.15). However, while patients with high-concern are more likely to have clinically significant disease (Applicant 2016), there is no evidence that being of high-concern will impact the diagnostic accuracy of mpMRI.

The included studies used a 1.5T and/or 3.0T MRI machines. All key studies used the PI-RADS system for image analysis. Where reported, all studies used gadolinium based contrast agents (Lista et al. 2015; Wang et al. 2015).

The comparator described in the Protocol was TRUSGB or TPUSGB in combination with PSA/DRE and clinical judgement or PSA/DRE and clinical judgement alone in men who opt to not have a biopsy.

The reference standard in the Protocol was the pathological analysis of the biopsy obtained samples. Pathology of samples obtained from biopsy was used as a reference standard (and assumed to be accurate) by all included studies. As discussed in Subsection B3.1; biopsy is not a perfect reference standard. TRUSGB was used alone or in combination with cores taken from MRI-suspicious regions using either cognitive guidance (C-MRIGB) or using MRI and US fusion guided biopsy (MRI/US FGB). As the use of MRIGB was not a comparator listed in the Protocol, subgroups analysis was performed (Subsection B3.6) to estimate the effect, if any, this deviation had on the diagnostic accuracy results.

Table 20 Selected characteristics of the key diagnostic accuracy studies for Population 1

Trial/Study Country Prospective or retrospective?	n Age (years)	Basis for inclusion PSA level (ng/ml) PSA density (ng/ml²) % Prior negative biopsy	MRI details: T Coil Contrast	Biopsy details: Type?
Abd-Alazeez et al. (2014) UK Prospective	54 Median 64 (range 39-75)	High or increasing PSA Median 10 (range 2-23) Density NR 100%	1.5 or 3.0T PPAC Gadoterate meglumine	TRUS + C- MRIGB
Baldisserotto et al. (2016) Brazil Retrospective	54 Mean 65.9 (range 53-81)	Concerning PSA and/or DRE Mean 8.4 (range 3-31) Mean 0.16 (SD 0.14) NR	3.0T PPAC NR	TRUS + C- MRIGB
Baur et al. (2016) Germany Prospective	45 Mean 66 (range 46-81)	Concerning PSA and/or DRE Mean 12.3 (range 5.2-70) NR 100%	3.0T PPAC Gadobutrol	TRUS/MRI FGB
Dikaios et al. (2015) UK Retrospective	85 Mean 63 (range 45-77)	Concerning PSA and/or DRE Mean 8.39 (range 1.2-40) NR NR	1.5T PPAC NR	Template
Jambor et al. (2014) Finland Retrospective	55 Median 66 (range 47-76)	PSA >4 ^c Median 7.4 (range 4-14) NR 0%	3.0T BAC + SAC Gadoterate meglumine or Gadobutrol	TRUS + C- MRIGB
Lista et al. (2015) Spain Prospective	150 Mean 66 (SD 5)	PSA >4ng/ml Mean 11.3 (range 0.9-75) NR 100%	1.5T ERC + pelvic antenna NR	TRUSGB
Pokorny et al. (2014) Australia Prospective	226 ^a Median 63 (IQR 57-68)	Concerning PSA and/or DRE Median 5.3 (IQR 4.1-6.6) NR NR	3.0T NR (no ERC) NR	TRUSGB
Thompson et al. (2014) Australia Prospective	150 Median 62.4 (IQR 55-66.4)	Concerning PSA and/or DRE Median 5.6 (IQR 4.5-7.5) NR NR	1.5 or 3.0T NR (no ERC) Gadopentetic acid	TRUS + C- MRIGB

Trial/Study Country Prospective or retrospective?	n Age (years)	Basis for inclusion PSA level (ng/ml) PSA density (ng/ml ²) % Prior negative biopsy	MRI details: T Coil Contrast	Biopsy details: Type?
Thompson et al. (2016) Australia Prospective	344 Median 62.9 (IQR 55.9- 67.1)	Concerning PSA and/or DRE Median 5.2 (IQR 3.7-7.1) NR 0%	1.5 or 3.0T NR (no ERC) Gadopentetic acid	TRUS + C- MRIGB
Wang et al. (2015) China NR	586 ^b Mean 70.0 (SD 8.3)	Concerning PSA and/or DRE and/or family history PSA 0-4: n=132, PSA 4.01-10: n=345 PSA >10: n=587 PSA NR: n=49 PSA density: NR Prior negative biopsy: NR	1.5T PPAC + ERC Gadopentetic acid	TRUSGB
Zhao et al. (2016) China Retrospective	372 Mean 68.5 (SD 9.2)	Concerning PSA and/or DRE Mean 15 (SD 13.3) NR NR	3.0T BAC NR	TRUS + C- MRIGB

^a: 3 patents in Pokorny et al. (2014) withdrew and were not included in the analysis.

^b: Wang et al. (2015) enrolled 1,113 patients into the study but only 586 received the reference standard and were included in the analysis. Baseline characteristics were only reported for the entire cohort of 1,113 patients.

^c: Jambor et al. (2015) excluded patients with an abnormal DRE result.

BAC = body array coil, C-MRIGB = cognitive MRI guided biopsy, PPAC = pelvic phased array coil, ERC = endorectal coil, SAC = spine array coil, NR = not reported, SD = standard deviation, UK = United Kingdom, T = Tesla, C-MRIGB = cognitive MRI guided biopsy, TRUS = trans-rectal ultrasound, GB = guided biopsy, FGB = fusion guided biopsy, PSA = prostate specific antigen.

B3.5 OUTCOME MEASURES AND ANALYSIS: DIAGNOSTIC ACCURACY (POPULATION 1)

To assess the diagnostic accuracy of the proposed test, key studies were only included if they provided data that could be extracted into a classic 2 x 2 table, in which the results of the index test were cross-classified against the results of the reference standard,² and Bayes' Theorem was applied (Table 21).

² Armitage, P, Berry, G & Matthews, JNS 2002, *Statistical methods in medical research*, fourth edn., Blackwell Science, Oxford.

Table 21 Diagnostic accuracy data extraction

		Reference standard		
		Disease +	Disease –	
Index test	Test +	true positive	false positive	Total test positive
Or comparator	Test –	false negative	true negative	Total test negative
		Total with disease	Total without disease	

The primary outcomes reported by all of the key studies, were the sensitivity and specificity of mpMRI in the detection of PCa of any severity.³

Only studies that provided per-patient data were included in the meta-analysis as the decision whether to perform a biopsy is made on a per-patient basis in the clinical algorithm. Abd-Alazeez et al. (2014) was not included in the meta-analysis as results in this study were presented per hemisphere. No other key study was excluded from the meta-analysis.

As a secondary outcome, the sensitivity and specificity of mpMRI for the diagnosis of clinically significant cancer was calculated. Where studies reported this outcome, the definition used by the authors was extracted. Other studies reported the diagnostic accuracy of mpMRI by Gleason score of the identified tumours. From these studies, a Gleason score ≥ 7 was considered clinically significant and this data was also included in the secondary analysis.

The bivariate model and hierarchical summary receiver operating characteristic (HSROC) analyses were conducted for Population 1. The mixed modelling approach described by Reitsma et al. (2005) was used to provide estimated summaries of sensitivity and specificity and the corresponding 95 per cent confidence ellipses (Reitsma et al. 2005). The HSROC curve described by Rutter and Gatsonis (2001) was generated and the associated area under the curve (AUC) was compared across imaging techniques (Rutter and Gatsonis 2001). Heterogeneity was estimated using visual inspection of the prediction interval.

A priori, it was determined that the following subgroups would be investigated: use of an endorectal coil, type of biopsy and prospective versus retrospective studies. *Post-hoc* subgroup analyses were performed on PI-RADS version 1 versus version 2.

Estimates of sensitivity and specificity were performed for the detection of any type of cancer and for the detection of clinically significant cancer (as defined by the study or defined as Gleason ≥ 7).

³ Deeks, JJ 2001, 'Systematic reviews of evaluations of diagnostic and screening tests', in M Egger, G Davey Smith & DG Altman (eds), *Systematic Reviews in Healthcare: Meta-Analysis in Context*, second edn, BMJ Publishing Group, London, pp. 248–282.

Meta-analyses were conducted in R i386 v3.1.2 using the “mada” package (Doebler and Holling 2012). Publication bias was not assessed due to the inherent difficulty in estimating publication bias for diagnostic studies and inaccuracy in interpretation of results (Macaskill et al. 2010).

B3.6 RESULTS OF THE SYSTEMATIC LITERATURE REVIEW: DIAGNOSTIC ACCURACY (POPULATION 1)

IS MPMRI ACCURATE?

Summary – What is the diagnostic accuracy of mpMRI compared to biopsy in patients with a suspicion of prostate cancer?

Ten studies, including 2,062 patients, were identified that reported a per-patient analysis of the diagnostic accuracy of mpMRI in patients suspected of having PCa based on concerning PSA or DRE results. Pathology of samples obtained by biopsy was the reference standard in all studies. There were no applicability issues identified between the included key studies and the proposed population in the Protocol. Only studies using a threshold for PI-RADS scoring consistent with that stated in the Protocol (PI-RADS ≥ 4 for a positive result) were included in this analysis.

For the detection of any cancer, mpMRI has a sensitivity of 73.4% (95% CI [57.0, 85.1]) and a specificity of 77.1% (95% CI [63.5, 86.7]) – results from meta-analysis of 10 studies including 2,062 patients.

For the detection of clinically significant cancer mpMRI has a sensitivity of 76.3% (95% CI [58.6, 88.0]) and a specificity of 82.9% (95% CI [71.5, 90.4]) (results from meta-analysis of 6 studies including 1,229 patients).

The point estimates for sensitivity and specificity are associated with wide confidence intervals reflecting uncertainty in the results. Heterogeneity in the evidence base was high, particularly for studies reporting the diagnosis of any cancer and could not be explained through subgroup analysis of clinical features.

The quality for the diagnostic accuracy outcomes was rated as ‘poor’ using the GRADE tool. This reflects serious issues with the precision and consistency in the evidence base.

Diagnostic accuracy data from the 10 key studies for Population 1 are reported in Table 22. The studies were judged to be clinically homogenous on the basis of similar patient enrolment criteria and index test characteristics with the use of a consistent threshold. On this basis a meta-analysis of the results was undertaken. A summary of the estimates of sensitivity and specificity generated from meta-analysis of the studies using the bivariate model are provided in Table 23.

Table 22 Results of key accuracy trials comparing mpMRI against biopsy

Study ID	Study characteristics	Result – any cancer	Result - clinically significant cancer	Definition of clinically significant cancer
Baldisserotto et al. (2016)	Retrospective No ERC TRUSGB + C-MRIGB PI-RADS v2	Sensitivity=73% Specificity=81%	NR	NA
Baur et al. (2016)	Prospective No ERC TRUS/MRI FGB PI-RADS v1	Sensitivity=93% Specificity=59%	NR	NA
Dikaios et al. (2015)	Retrospective No ERC Template biopsy PI-RADS v1	Sensitivity=30% Specificity=86%	Sensitivity=36% Specificity=90%	≥ Gleason 7 (any pattern) or template biopsy cancer core length ≥4mm
Jambor et al. (2014)	Retrospective No ERC TRUSGB + C-MRIGB PI-RADS v1	Sensitivity=78% Specificity=39%	Sensitivity=91% Specificity=50%	≥ Gleason 7 (any pattern) or template biopsy cancer core length ≥3mm or tumour volume >0.5ml or tumour stage ≥ pT3
Lista et al. (2015)	Prospective ERC TRUSGB PI-RADS v1	Sensitivity=93% Specificity=38%	NR	NA
Pokorny et al. (2014)	Prospective No ERC TRUSGB PI-RADS v1	Sensitivity=68% Specificity=76%	Sensitivity=84% Specificity=74%	Gleason ≥7 (any pattern) – researcher calculated in line with definitions from other studies that designated Gleason 7 to be significant.
Thompson et al. (2014)	Prospective No ERC TRUSGB + C-MRIGB PI-RADS v1	Sensitivity=40% Specificity=91%	Sensitivity=67% Specificity=92%	Gleason 7 with >5% Gleason grade 4 and less than 50% cores positive OR Gleason 6-7 with <5% Gleason grade 4 with >30% cores OR cancer core length >8mm OR Gleason score 7 with >5% Gleason grade 4 OR Gleason 8-10.
Thompson et al. 2016	Prospective No ERC TRUSGB + C-MRIGB PI-RADS v1	Sensitivity=53% Specificity=90%	Sensitivity=69% Specificity=86%	Gleason 7 with >5% Gleason grade 4 and less than 50% cores positive OR Gleason 6-7 with <5% Gleason grade 4 with >30% cores OR cancer core length >8mm OR Gleason score 7 with >5% Gleason grade 4 OR Gleason 8-10.
Wang et al. (2015)	NR if prospective ERC TRUSGB PI-RADS v1	Sensitivity=90% Specificity=80%	NR	NA

Study ID	Study characteristics	Result – any cancer	Result - clinically significant cancer	Definition of clinically significant cancer
Zhao et al. (2016)	Retrospective No ERC TRUSGB + C-MRIGB PI-RADS v2	Sensitivity=80% Specificity=90%	Sensitivity=85% Specificity=83%	Gleason ≥ 7 (any pattern) – researcher calculated.

ERC = endorectal coil, TRUSGB = trans-rectal ultrasound guided biopsy, C-MRIGB = cognitive MRI-guided biopsy, NR = not reported, NA = not applicable, PI-RADS = Prostate Imaging Reporting and Data System.

Table 23 Summary of findings for the accuracy of mpMRI, relative to biopsy, in patients with suspected prostate cancer with assumed pre-test probability (prevalence) of 35%

Outcomes	mpMRI – all cancer	mpMRI – clinically significant cancer	Quality of evidence ^a	Importance
Sensitivity % [95% CI]	73.4 [57.0, 85.1]	76.3 [58.6, 88.0]	⊕⊕⊖⊖ Low ^{1,2}	Critical
Specificity % [95% CI]	77.1 [63.5, 86.7]	82.9 [71.5, 90.4]	⊕⊕⊖⊖ Low ^{1,2}	Critical
PPV % [95% CI]	77.2 [63.4, 86.8]	74.7 [69.4, 79.3]	⊕⊕⊖⊖ Low ^{1,2}	Important
NPV % [95% CI]	72.8 [57.2, 84.2]	83.5 [78.8, 87.4]	⊕⊕⊖⊖ Low ^{1,2}	Important

^a: GRADE Working Group grades of evidence (Guyatt et al. 2013).

⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.

⊕⊕⊕⊖ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

⊕⊕⊖⊖ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

⊕⊖⊖⊖ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

¹: No explanation for the observed heterogeneity could be found.

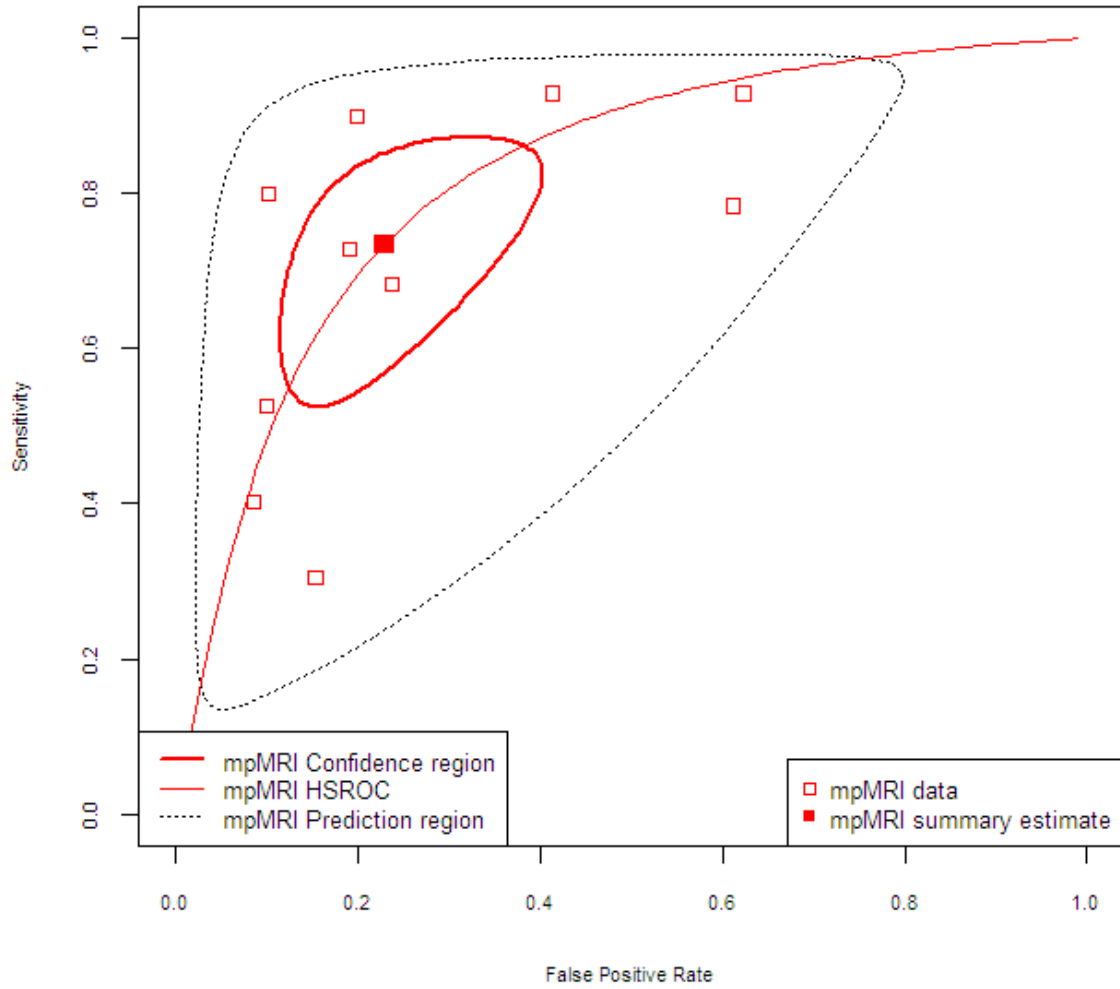
²: The wide confidence interval reflects imprecision.

CI = confidence interval, PPV = positive predicative value, NPV = negative predicative value.

DIAGNOSIS OF ANY CANCER

In the diagnosis of any cancer, mpMRI was estimated to have a sensitivity of 73.4 per cent (95% CI [57.0, 85.1]) and a specificity of 77.1 per cent (95% CI [63.5, 86.7]). The wide confidence intervals reflect uncertainty around this estimate. The Hierarchical Summary Receiver Operating Characteristic (HSROC) curve and summary estimate with 95 per cent confidence region and 95 per cent prediction region is provided in Figure 7. The wide prediction region illustrates the high level of heterogeneity present in the evidence base.

Figure 7 HSROC curve and bivariate model results for the diagnosis of any cancer by mpMRI in Population 1.



Subgroup analysis was undertaken to explore the possible causes of the observed heterogeneity; however, no cause was identified. Results from this analysis are presented in Table 24.

Table 24 Subgroup and sensitivity analysis for the diagnostic accuracy of mpMRI in Population 1

Subgroup	Patients/Studies	Sensitivity (%) [95% CI]	Specificity(%) [95% CI]
All studies	2,062 patients (10 studies)	73.4 [57.0, 85.1])	77.1 [63.5, 86.7]
Endorectal coil	736 patients (2 studies)	91.5 [86.8, 94.7]	61.0 [19.6, 90.9]
No Endorectal coil	1,326 patients (8 studies)	67.6 [54.6, 78.3]	80.4 [67.5, 89.0]
Biopsy with MRI	1,018 patients (6 studies)	70.3 [52.6, 83.4]	80.1 [61.5, 91.0]
Systematic biopsy	1,044 patients (4 studies)	76.9 [40.8, 94.1]	72.1 [48.5, 87.7]
Prospective	910 patients (5 studies)	71.6 [47.2, 87.7]	75.2 [50.1, 90.1]
Retrospective	1,152 patients (5 studies)	73.6 [50.8, 88.3]	78.7 [61.2, 89.6]
PI-RADS version 1	1,636 patients (8 studies)	72.7 [51.4, 87.0]	74.6 [57.5, 86.5]
PI-RADS version 2	426 patients (2 studies)	77.5 [68.5, 84.5]	87.2 [76.5, 93.4]
Dikaios et al. (2015) removed	1,977 patients (9 studies)	77.0 [62.8, 86.9]	76.1 [60.8, 86.7]

CI = confidence interval, PI-RADS = Prostate Imaging Reporting and Data System.

Subgroup analysis suggests that use of an endorectal coil may improve the sensitivity mpMRI. However, this estimate is based on only two studies and the wide confidence intervals associated with the point estimate for specificity in this subgroup indicates considerable uncertainty. As such, it would not be appropriate to draw any conclusions from this result.

There was no statistically significant difference in estimates of sensitivity and specificity between the studies that used PI-RADS version 1 compared to version 2, although only two studies reported use of PI-RADS version 2. Similarly, no significant difference was observed between studies using prospective or retrospective study designs.

A sensitivity analysis was performed by removing the study by Dikaivos et al. (2015) on the basis that the study focused on the use of mpMRI to identify PCa in the transition zone. It was hypothesized that it may have different sensitivity than studies diagnosing cancer of the peripheral and transition zones. While the removal of the results by Dikaivos et al. (2015) does improve the estimate of sensitivity of mpMRI at the expense of the specificity, the results are not statistically different. A conservative approach was taken and the estimates of sensitivity and specificity from the full cohort of studies have been used to inform the results of this review.

The point estimates calculated in the meta-analysis must be viewed in light of the fact that biopsy is not a perfect reference standard. This assessment has used the 81 per cent point estimate for any cancer as the TRUSGB sensitivity estimate (Schoots et al. 2015) (Subsection B3.1). The overall impact of the less than perfect nature of biopsy as a reference standard is unable to be quantified; however, this adds further uncertainty to the point estimates generated from the meta-analyses.

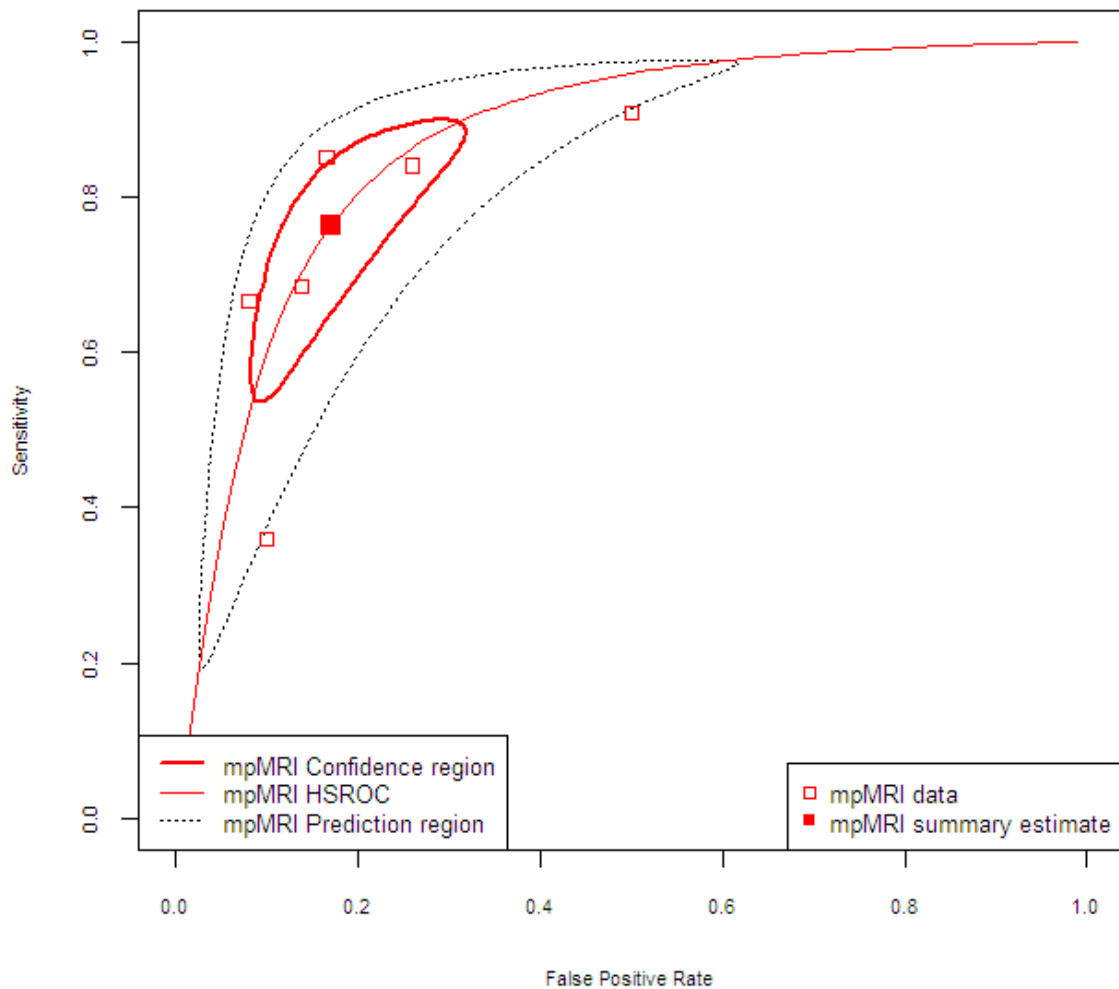
DIAGNOSIS OF CLINICALLY SIGNIFICANT CANCER

Six studies, including 1,229 patients also investigated the ability of mpMRI to diagnose clinically significant cancer (Dikaivos et al. 2014; Jambor et al. 2014; Pokorny et al. 2014; Thompson et al. 2014; Thompson et al. 2016; Zhao et al. 2016). Clinically significant cancer was defined slightly differently by each of the studies; however, most studies considered a Gleason ≥ 7 to be clinically significant. Where the study did not analyse results for clinically significant cancer separately, but data by Gleason score was available, the researchers extracted data on the diagnosis of tumours with a Gleason score ≥ 7 .

For the diagnosis of clinically significant cancer, mpMRI was found to have a sensitivity of 76.3 per cent (95% CI [58.6, 88.0]) and a specificity of 82.9 per cent (95% CI [71.5, 90.4]). The HSROC curve and summary estimate with 95 per cent confidence region and 95 per cent prediction region is provided in Figure 8. Wide confidence intervals reflect uncertainty associated with the point estimate. The accuracy of mpMRI in the detection of clinically significant PCa was not statistically different to its accuracy at detecting PCa of any severity.

No subgroup analyses were undertaken due to the smaller number of studies available. However, as shown in Figure 8, less heterogeneity was observed for the subset of studies reporting diagnosis of clinically significant cancer than for studies reporting diagnosis of any cancer.

Figure 8 HSROC curve and bivariate model results for the diagnosis of clinically significant cancer by mpMRI in Population 1



B3.7 EXTENDED ASSESSMENT OF RELIABILITY EVIDENCE (POPULATION 1)

Due to the observed heterogeneity in the diagnostic accuracy analyses, with no apparent clinical cause, an assessment of reliability was deemed necessary.

The term 'reliability' (which is analogous to the concept of 'precision') refers to the amount of agreement of different operators or instruments applying the same investigative medical service. That is, a reliable investigative medical service is measuring something consistently.

Inter-reader reliability data was extracted from key studies. In addition, a targeted search was performed in PubMed and EMBASE for any additional studies that measured the reliability of mpMRI

using PI-RADS as a primary outcome, or which measured any learning curve associated with the use of PI-RADS as a primary outcome.

The medical literature was searched on 20 June 2016 to identify relevant studies. The search was not date limited. Search terms are described in Table 25.

Table 25 Search terms used (PubMed platform)

Element of clinical question	Search terms
Population	(prostate) OR prostate[MeSH Terms]
Intervention	(((((PI-RADS) OR PIRADS) OR multiparametric MRI) OR mp-MRI) OR multiparametric-MRI) OR mp MRI) OR mpMRI) OR ((prostate imaging and reporting data system)))
Comparator (if applicable)	NA
Outcomes (if applicable)	((((inter-rater) OR reliability) OR reproducibility) OR kappa))
Limits	None

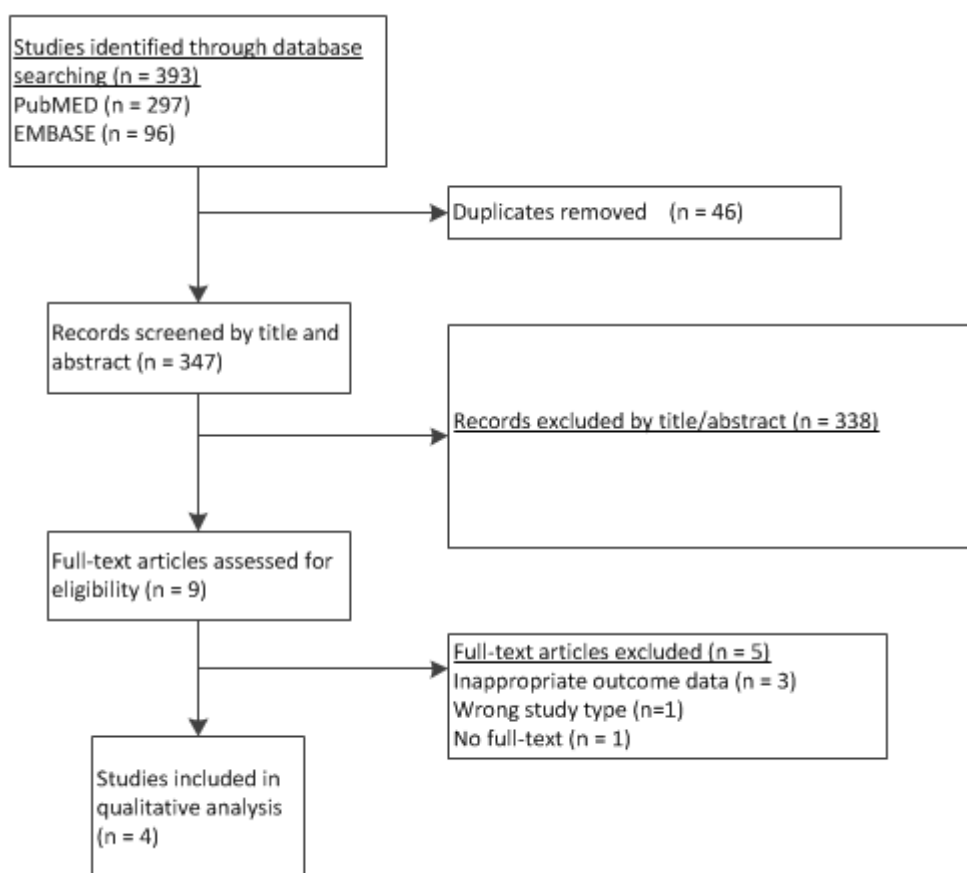
NA = not applicable, PI-RADS = Prostate Imaging Reporting and Data System, mpMRI = multiparametric magnetic resonance imaging.

The PRISMA flowchart (Liberati et al. 2009) included at Figure 9 provides a graphic depiction of the results of the literature search and the application of the study selection criteria as listed in Box 5 (Subsection A9).

The single reviewer who screened studies by title and abstract also completed the full text assessment.

All other studies that met the inclusion criteria are listed in Appendix C. Studies that could not be retrieved or that met the inclusion criteria but contained insufficient or inadequate data for inclusion are listed as excluded studies in Appendix E.

Figure 9 Summary of the process used to identify and select studies for the assessment of reliability



Five of the key diagnostic accuracy studies for Population 1 reported Cohen’s kappa (κ) to describe inter-reader reliability. The kappa values range from 0.48-0.81, with a median value of 0.63.

Four additional studies were identified which investigated the inter-reader reliability of PI-RADS as a primary outcome and/or any learning curve associated with use of the PI-RADS system (Table 26) (Garcia-Reyes et al. 2015; Muller et al. 2015; Rosenkrantz et al. 2016; Rosenkrantz et al. 2013a).

Rosenkrantz et al. (2013) reported inter-reader agreement for three readers (two with 4-6 years prostate MRI interpretation, one who was inexperienced) using PI-RADS version 1 on mpMRI images from 55 patients. The overall kappa between the two experienced readers (reader 1 and 2) was 0.609. Agreement between the experienced readers and the inexperienced reader was lower ($\kappa=0.477$ and 0.340).

Rosenkrantz et al. (2016) reported moderate inter-reader agreement (overall $\kappa=0.552$) when PI-RADS version 2 was used with a 4 or 5 score classified as a positive result. The retrospective study included a review of mpMRI images from 120 patients by six radiologists based at six different centres.

Muller et al. (2015) report inter-reader agreement for five readers reviewing images from 101 biopsy naïve patients using PI-RADS version 2. The overall Kendall’s tau (τ) was 0.46.

Two studies were identified which investigated the impact of a possible learning curve associated with the use of PI-RADS. Rosenkrantz et al. (2016) found no learning curve amongst readers experienced in mpMRI of the prostate. Garcia-Reyes et al. (2015) found a dedicated training program improved the accuracy of readers with limited experience from 74.2 per cent to 87.7 per cent when re-reviewing the same set of images from 31 patients following a memory extinction period.

Table 26 Results of reliability trials

Study ID	Study characteristics	Summary of reliability results
Baldisserotto et al. (2016) ^a	2 urologists: with 1 or 10 years' experience.	$\kappa=0.53$
Baur et al. (2016) ^a	2 readers with 3 or 5 years' experience in prostate imaging.	$\kappa=0.73$
Thompson et al. (2014) ^a	2 radiologists each with >1000 prior prostate mpMRIs.	$\kappa=0.63$
Wang et al. (2015) ^a	2 radiologists each with >1000 prior prostate mpMRIs.	$\kappa=0.81$
Zhao et al. (2016) ^a	2 radiologists experienced in PI-RADS v2.	$\kappa=0.48$
Rosenkrantz et al. (2013) ^b	Three readers – 2 with 4-6 years prostate MRI experience 1 reader who was inexperienced at reading prostate MRI.	κ reader 1 & 2=0.609 κ reader 1 & 3=0.477 κ reader 2 & 3=0.340
Rosenkrantz et al. (2016) ^b	Six readers at six centres. All readers had 4-9 years post-fellowship experience and a special interest in prostate MRI imaging.	Overall $\kappa=0.552$ No evidence of a learning curve
Muller et al. (2015) ^b	Five readers with varying levels of experience (250 – 4000 mpMRI prostate examinations).	Overall $\tau=0.46$
Garcia-Reyes et al. (2015) ^b	Five readers with ~ 12 months experience in abdominal imaging (<50 cases of prostate MRI).	Accuracy pre-training 74.2% Accuracy post-training 87.7%

^a: Key accuracy study.

^b: Identified through targeted search.

mpMRI = multiparametric MRI, MRI = magnetic resonance imaging, κ = Cohen's kappa, τ = Kendall's tau.

Overall, kappa values from 0.34-0.81. Results from key diagnostic accuracy studies were consistent with results from studies seeking to measure the inter-reader reliability of mpMRI using PI-RADS. The results reported in Table 26 suggest reliability may be an issue for use of mpMRI with PI-RADS (both version 1 and 2) and this may therefore explain the observed heterogeneity in the estimates of sensitivity and specificity.

There may also be a learning curve associated with the use of PI-RADS; however, we do not believe the results of our meta-analysis have been significantly influenced by any learning curve as eight key studies reported use of experienced readers. Jambor et al. (2014) and Lista et al. (2015) did not report reader experience. This would be consistent with results from Rosenkrantz et al. (2016) who reported that for experienced readers no learning curve was apparent.

The issue of inter-reader reliability of PI-RADS has been the subject of a recent commentary by (Rosenkrantz and Margolis 2016). In this commentary, the evident variability in reported kappa values in peer-reviewed literature was noted. The importance of intense training in PI-RADS and the need to adopt rigorous quality assurance methods including auditing of performance were highlighted. Should the proposed item be listed on the MBS, institutions offering the service may need to consider the adoption of training and auditing programs.

B3.9 INTERPRETATION OF EVIDENCE ON DIAGNOSTIC PERFORMANCE (POPULATION 1)

In summary, meta-analysis of 10 studies including 2,062 patients found that for the detection of PCa of any severity, mpMRI has a sensitivity of 73.4 per cent (95% CI [57.0, 85.1]) and a specificity of 77.1 per cent (95% CI [63.5, 86.7]) .

For the detection of clinically significant cancer mpMRI has a sensitivity of 76.3 per cent (95% CI [58.6, 88.0]) and a specificity of 82.9 per cent (95% CI [71.5, 90.4]) (results from meta-analysis of 6 studies including 1,229 patients).

The point estimates for sensitivity and specificity are associated with wide confidence intervals reflecting uncertainty in the results. Heterogeneity in the evidence base was high and could not be explained through subgroup analysis. The uncertainty associated with the point estimates is potentially due to issues with the reliability of mpMRI. Overall, moderate reliability has been reported in studies investigating inter-reader agreement amongst multiple readers using the PI-RADS system for mpMRI interpretation.

The point estimates for sensitivity and specificity of mpMRI may also have been influenced by the underlying diagnostic accuracy of the biopsy used to obtain reference standard samples. This was not able to be quantified but it should be noted that TRUSGB and TPUSGB are not 100 per cent accurate in the detection of PCa.

The quality of the evidence base for each of the diagnostic accuracy outcomes was rated as 'poor' using the GRADE tool. This rating reflects the serious issues with the precision and consistency of the meta-analysis results. In light of the results of the analysis of diagnostic performance and the uncertainties regarding reliability, there is no evidence that mpMRI is superior to TRUSGB or TPUSGB. This applies to the detection of PCa of any severity and to the detection of clinically significant cancer.

B4 CLINICAL VALIDITY

An analysis of clinical validity was not required for this assessment.

B5 CLINICAL UTILITY

B5.1 IMPACT ON CLINICAL MANAGEMENT (THERAPEUTIC EFFICACY) (POPULATION 1)

Based on the current and proposed clinical algorithm (Figure 1 and Figure 2, Subsection A6), the results of the mpMRI lead to four clinical scenarios:

In low-concern patients:

1. If mpMRI is PI-RADS 1-3 (true negative or false negative) – the patient will avoid a biopsy under the proposed algorithm instead of undergoing a TRUSGB or TPUSGB under the current algorithm.
2. If mpMRI is PI-RADS 4 or 5 (true positive or false positive) – the patient will undergo an MRIGB guided biopsy instead of a TRUSGB.

In high-concern patients:

1. If mpMRI is PI-RADS 1-3 (true negative or false negative) – the patient will undergo a template biopsy. In this scenario there is no change from current management so there will be no impact on therapeutic effectiveness.
2. If mpMRI is PI-RADS 4 or 5 (true positive or false positive) – the patient will undergo an mpMRI guided biopsy instead of a TRUSGB.

No studies were identified that investigated change in management associated with the introduction of mpMRI for patients in Population 1.

For men with a suspicion of prostate cancer, treatment decisions are made based on biopsy results. Under the proposed management algorithms, mpMRI results will determine if patients should receive a biopsy. For men with suspected prostate cancer a PI-RADS score less than or equal to 3 will result in low-concern patients avoiding a biopsy; the therapeutic effect of this biopsy avoidance is discussed in Section B5.2. High-concern patients with a PI-RADS score less than or equal to 3 will receive a systematic biopsy under current and proposed management algorithms.

Patients with a PI-RADS score of 4 or 5 will have a change in the type of biopsy they receive (change from TRUSGB or TPUSGB to MRIGB). Any change in management associated with this change in biopsy is the subject of Application CA 1424. The Assessment Group for CA 1424 has advised that no studies investigating the change in management associated with changing from an US to a MRI guided biopsy were identified. In addition, the Assessment Group for CA 1424 has advised that no peer-reviewed literature has been identified investigating safety differences between biopsy guidance techniques. Similarly, our own searches into the safety of prostate biopsy (Subsection B7)

have not identified any literature on this topic. There is no evidence that safety outcomes are different for trans-rectal biopsy performed under US or MRI guidance.

A recent systematic review by Schoots et al. (2015) compared TRUSGB to MRIGB. This review determined that there is no difference in the diagnostic accuracy of USGB and MRIGB (cognitive, US/MRI fusion or in-gantry techniques) in the detection of prostate cancer.⁴ The equivalent diagnostic accuracy of the biopsy techniques suggests there will be no associated change in management.

B5.2 THERAPEUTIC EFFECTIVENESS (INCLUDING IMPACT OF EFFECT MODIFICATION) (POPULATION 1)

Low-concern patients: advice from the Applicant is that 30-40 per cent of patients will have PCa and a total of 5-10 per cent will have clinically significant cancer (which equates to 13-33% of cancers being clinically significant).

mpMRI True positive: These patients have PCa and will receive a biopsy to guide the treatment decision. Under current management these patients will receive a TRUSGB or TPUSGB. Under the proposed algorithm these patients will receive MRIGB. Using the approach recommended by Merlin and Leman (Merlin et al. 2013), no investigation of therapeutic effectiveness has been undertaken as management of these patients is unlikely to change under the proposed algorithm owing to the equivalent safety and accuracy of the biopsy types. Current treatment options for patients following biopsy may include AS of low/intermediate risk disease, radical prostatectomy, radiation therapy, androgen deprivation therapy, brachytherapy, high intensity focused US and/or chemotherapy (Evans et al. 2013).

mpMRI False positive: These patients do not have PCa but have been incorrectly identified as having cancer by mpMRI. Under current management these patients will receive a TRUSGB or TPUSGB. Under the proposed management these patients will receive MRIGB. It is expected that biopsy of any type will correct the misdiagnosis by mpMRI and these patients will not receive unnecessary treatment. There will be no change in therapeutic effectiveness should the proposed items be listed. No further investigation of therapeutic effectiveness for this scenario has been undertaken.

⁴ There was no difference between cognitive-MRIGB and TRUSGB for detection of clinically significant cancer. While the review found that MRI/US fusion guided biopsy may have a greater diagnostic accuracy than TRUSGB in the detection of clinically significant cancer, the authors of the review also detail a number of issues with this result and state that it might be methodologically incorrect to conclude that MRIGB finds more high-grade cancer than TRUSGB. Therefore, in this assessment, only results on the detection of all cancer types have been used as these were considered at less risk of bias and are informed by a larger evidence base.

mpMRI True negative: These patients do not have PCa and have been accurately diagnosed by mpMRI. These patients will avoid having a biopsy and therefore avoid the adverse events associated with biopsy. The adverse events are discussed in Subsection B7.

mpMRI False negative: These patients have PCa but have been incorrectly diagnosed as cancer free by mpMRI. These patients will avoid the adverse events associated with biopsy as described in Subsection B7; however, there will be a delay in the diagnosis of their disease. According to the clinical algorithm for the proposed service, these patients will be re-evaluated six months after the negative mpMRI; though some patients may face additional delays. The impact of delayed treatment for this group of patients has been investigated (Subsection B5.2.6). Advice from the Applicant is that most (67-87%) of these patients will have low risk disease.

High-concern patients: advice from the Applicant is that 50 per cent of these patients will have PCa 90 per cent of which will be clinically significant. As all high-concern patients will receive a biopsy, regardless of the results of the mpMRI, no change in management and no changes to therapeutic effectiveness are expected for this population.

B5.2.1 LITERATURE SOURCES AND SEARCH STRATEGIES: THERAPEUTIC EFFECTIVENESS (POPULATION 1)

A literature search was conducted to identify studies that investigated patient outcomes associated with a delay to PCa treatment.

The medical literature was searched on 24 June 2016 to identify relevant studies. The search was not date limited. Searches were conducted in the PubMed database. Search terms are described in Table 27.

Table 27 PubMed search strategy

Element of clinical question	Search terms
Population	(prostate) OR prostate[MeSH Terms]
Intervention	((((deferred[Title/Abstract] OR delay[Title/Abstract])) AND (((therapy[Title/Abstract] OR treatment[Title/Abstract] OR surgery[Title/Abstract] OR prostatectomy[Title/Abstract]))) OR (((((((((((("false negative"[Title/Abstract] OR false negative[Title/Abstract] OR missed diagnosis[Title/Abstract] OR untreated[Title/Abstract] OR "not treated"[Title/Abstract] OR "inappropriate treatment"[Title/Abstract] OR wrong diagnosis[Title/Abstract] OR misdiagnosis[Title/Abstract] OR false negatives[Title/Abstract] OR false negatives[Title/Abstract] OR false reassurance[Title/Abstract] OR inaccuracte[Title/Abstract] OR inaccurate[Title/Abstract]))))))))))
Comparator (if applicable)	NA
Outcomes (if applicable)	NA
Limits	None

NA = not applicable.

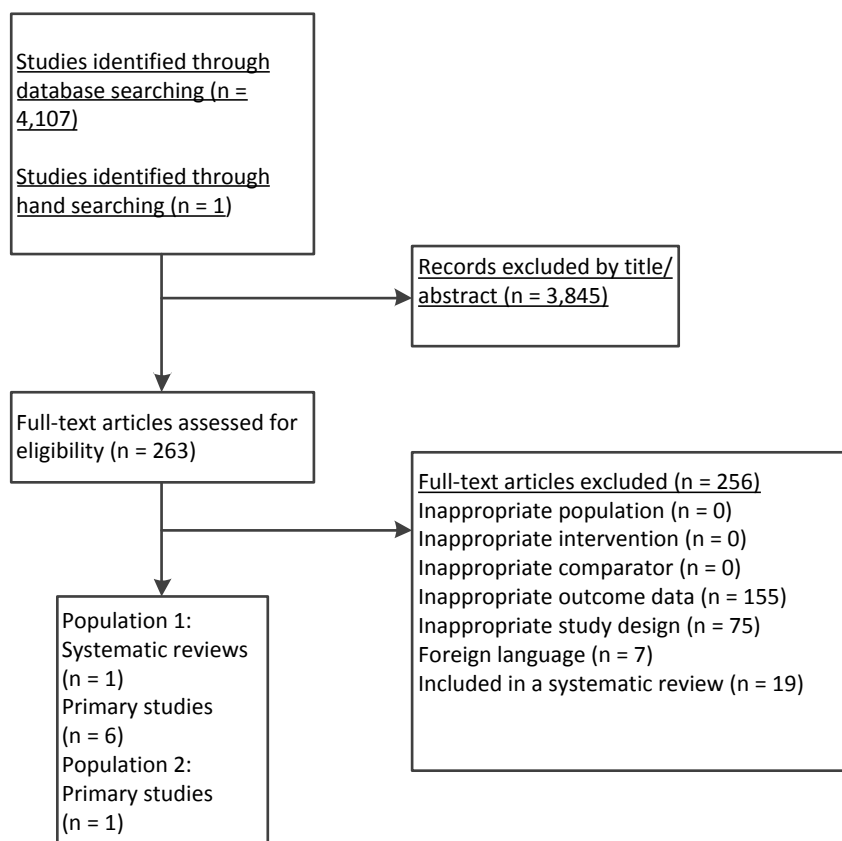
B5.2.2 RESULTS OF THE LITERATURE SEARCH: THERAPEUTIC EFFECTIVENESS (POPULATION 1)

The PRISMA flowchart at Figure 10 provides a graphic depiction of the results of the literature search and the application of the study selection criteria as listed in Box 7 (Subsection A9).

The single reviewer who screened studies by title and abstract also completed the full text assessment. All other studies that met the inclusion criteria are listed in Appendix C. Studies that could not be retrieved or that met the inclusion criteria but contained insufficient or inadequate data for inclusion are listed as Excluded Studies in Appendix E.

One systematic review was identified (van den Bergh et al. 2013). Only primary studies not included in this systematic review were included in the current analysis.

Figure 10 Summary of the process used to identify and select studies for the assessment of patient outcomes



B5.2.3 RISK OF BIAS ASSESSMENT: THERAPEUTIC EFFECTIVENESS (POPULATION 1)

Risk of bias of the systematic review was assessed using the AMSTAR tool (Shea et al. 2007). For the included primary studies the Downs and Black tool was used (Downs and Black 1998).

The systematic review by van den Bergh et al. (2013) failed to assess the quality of the included studies; it did not assess any publication bias, nor include grey literature, and did not provide a list of excluded studies. Therefore, this review is considered poor quality (Table 83, Appendix F). However, the review did provide adequate information about the included studies to enable data extraction and the methodological issues of the review were not considered to impact the conclusions of this assessment.

Overall, the primary studies were judged to have a moderate risk of bias (Table 84, Appendix F). The major limitations of the evidence base were the potential for confounding variables to influence the results and potential issues with applicability. The population included in most studies was entirely or mostly comprised of patients with low risk disease. Patients experiencing longer delays to treatment also tended to be men with low risk disease. It is unclear to what extent this influenced the results. Most studies measured the impact of a treatment delay of approximately three months. This is likely to be a shorter delay than patients in our target population would experience (expected to be ≥ 6 months). However, the studies by Dong et al. (2016) and Loeb et al. (2016) included treatment delays of greater than one year and included patients with low, intermediate and high risk disease (Dong et al. 2016; Loeb et al. 2016). Therefore, these studies were considered most applicable to this Assessment.

B5.2.4 CHARACTERISTICS OF THE EVIDENCE BASE

One systematic review (van den Bergh et al. 2013), including 17 studies with 34,517 patients and six primary studies (Boorjian et al. 2005; Dong et al. 2016; Eroglu et al. 2014; Loeb et al. 2016; O'Kelly et al. 2013; Redaniel et al. 2013) with an additional 32,504 patients, that assessed the impact of delayed treatment for PCa were identified. See Appendix C for details on the individual studies included in the evidence base. A summary of the trial characteristics of studies providing evidence relating to the health impact from the change in management is provided in Table 28.

The evidence base to inform the impact on a delay to treatment was diverse with respect to outcomes measured and study design. Length of delay as measured by the studies ranged from 2-24 months. Most studies (14/23) assessed the impact of a delay greater than three months compared to a delay less than three months. Five studies in the systematic review, as well as Dong et al. (2016), Loeb et al. (2016), and O'Kelly et al. (2013) assessed the impact of a delay greater than six months (Dong et al. 2016; Loeb et al. 2016; O'Kelly et al. 2013). These studies were considered most applicable to this assessment as it is unlikely that patients would be re-assessed within six months following an mpMRI.

Table 28 Key features of the included evidence assessing impact of delayed treatment in Population 1

Trial/Study	n	Design ^a / duration	Risk of bias	Patient population	Key outcome(s)	Result used in economic model
van den Bergh et al. (2013)	17 studies 34,517 patients	Systematic review of level III evidence Duration of primary studies NR	Moderate	Patients receiving radical local therapy – either prostatectomy, radiation therapy or both.	Survival, metastases formation, biochemical recurrence, extra-capsular extension, lymph node involvement, positive surgical margins, Gleason upgrade.	Used
Boorjian et al. (2005)	3,149	Prognosis level III-3 Median 5.4 years (IQR 2.2-7.9)	Moderate	Men with clinically localised PCa treated with radical prostatectomy.	Biochemical recurrence.	Used
Dong et al. (2016)	4,064	Prognosis level III-3 >12 months	Moderate	Men with clinically localised PCa treated with radiation therapy.	Survival, metastases formation, biochemical recurrence.	Used
Eroglu et al. (2014)	290	Prognosis level III-3 NR	Moderate	Men undergoing prostatectomy who's Gleason score at diagnosis was compared to at surgery .	Gleason upgrade.	Not used
Loeb et al. (2016)	7,608	Prognosis level III-3 Median 8.1 years	Moderate	Men with low risk PCa (Gleason ≤ 6) who entered an active surveillance protocol who subsequently were upgraded to Gleason ≥7.	Survival, extra-capsular extensions, positive surgical margins, Gleason upgrade.	Used
O'Kelly et al. (2013)	350	Prognosis level III-3 NR	Moderate	Men with low risk disease (Gleason ≤ 6, PSA <20 ng/ml, T1-2, Not N1, not M1).	Gleason upgrade.	Not used
Redaniel et al. (2013)	17,043	Prognosis level III-3 10 years	Moderate	Men who were referred to a specialist following a positive biopsy – outcomes associated with the delay in referral were analysed.	Survival.	Used

^a: NHMRC Level of evidence.

PSA = prostate specific antigen, TX = local spread of disease, N1 = lymph node involvement, M1 = metastatic disease, PCa = prostate cancer.

B5.2.5 OUTCOME MEASURES AND ANALYSIS: THERAPEUTIC EFFECTIVENESS (POPULATION 1)

See Appendix C for details on the outcomes measured in the included studies.

Due to the heterogeneous nature of the evidence base, no pooled statistical analysis was performed. Instead, results are discussed narratively below.

A difference in survival, metastatic disease, biochemical recurrence, extra-capsular extension, lymph node involvement and positive surgical margins was considered potentially clinically significant. Upgrade of tumour Gleason score in isolation of other outcomes was not considered clinically significant.

B5.2.6 RESULTS OF THE SYSTEMATIC LITERATURE REVIEW: THERAPEUTIC EFFECTIVENESS (POPULATION 1)

DOES THE CHANGE IN MANAGEMENT IMPROVE HEALTH OUTCOMES?

Summary – Does imaging with mpMRI improve health outcomes for men suspected of having prostate cancer?

Low-concern patients (50% of patient in Population 1)

mpMRI True positive: No evidence that patients with a true positive will experience any change in management or change to health outcomes was identified.

mpMRI False positive: No evidence that patients with a false positive will experience any change in management or change to health outcomes was identified.

mpMRI True negative: These patients will avoid having a biopsy and therefore avoid the adverse events associated with biopsy. The adverse events are discussed in Subsection B7.

mpMRI False negative: Patients will avoid the adverse events associated with biopsy as described in Subsection B7. However, these patients will be subject to a delay in the diagnosis of their disease. Systematic review of the literature has found little evidence that delays in treatment of up to 24 months will impact patient's health outcomes. This includes patients with high risk disease. These results are informed by one systematic review and six primary studies, all of which had a moderate/high risk of bias.

High-concern patients (50% of patient in Population 1)

All high-concern patients will undergo a biopsy under both current and proposed management algorithms. No evidence that patients who undergo a biopsy of any type will experience any change in management or change to health outcomes was identified.

Summary: based on the current and proposed clinical algorithms, most patients will not have any change to their management following introduction of mpMRI beyond a change in the type of biopsy they receive. There is no evidence that treatment decisions will be changed as a result of a change in biopsy technique. There is very limited evidence that for high risk disease a delay in treatment due to a false negative on mpMRI would

compromise patient outcomes; however, most evidence indicates a delay will not impact health outcomes regardless of disease risk. It should be noted that the evidence base for each outcome was rated as ‘very low’ when using the GRADE tool reflecting the observational nature of the included studies and the potential applicability issues of the included population.

As discussed above, only low-concern patients with a negative mpMRI will have a potential change to their health outcomes under the proposed algorithm.

For patients with a true negative result, health outcomes will be improved due to an avoidance of the adverse events associated with biopsy (discussed in Subsection B7).

Patients with a false negative result will avoid the adverse events associated with biopsy (discussed in Subsection B7). However, these patients will experience a delayed diagnosis of their disease. The summary of findings from the systematic literature review assessing the potential impact of this delay is shown in Table 29. The results from the individual studies, including those in van den Bergh et al. (2013), are reported in Appendix H.

Table 29 Summary of findings assessing whether a delay in treatment due to a false negative mpMRI changes patient outcomes in patients with prostate cancer

Outcomes	Impact of delay	Patients/Studies	Quality of evidence ^a	Importance
Overall survival follow-up range 5 to 8 years.	Delay did not impact overall survival (results from 5 studies).	41,146 patients (5 studies)	⊕○○○ VERY LOW ¹	Critical
Cancer free survival follow-up median 5 years.	Delay did not impact cancer free survival (results from 2 studies).	8,916 patients (2 studies)	⊕○○○ VERY LOW ^{1,2}	Critical
Rate of metastases formation follow-up range 38 to 120 months.	Delay did not impact rate of metastases formation (results from 4 studies).	6,681 patients (4 studies)	⊕○○○ VERY LOW ^{1,3}	Critical
Biochemical recurrence follow-up range 6 to 120 months.	3 studies reported recurrence was associated with delayed treatment, 11 studies reported no impact.	19,768 patients (14 studies)	⊕○○○ VERY LOW ¹	Critical
Extra-capsular extension follow-up range 27 to 97 months.	Delay did not impact rate of extra-capsular extension (results from 7 studies).	16,039 patients (7 studies)	⊕○○○ VERY LOW ¹	Important
Lymph node involvement follow-up range 38 to 120 months.	Delay did not impact rates of lymph node involvement (results from 3 studies).	3,605 patients (3 studies)	⊕○○○ VERY LOW ^{1,3}	Important

Outcomes	Impact of delay	Patients/Studies	Quality of evidence ^a	Importance
Positive surgical margins follow up range 6 to 97 months.	One study reported a delay >9 months was associated with an increase in the rate of positive surgical margins in patients with intermediate risk disease. 8 studies reported no impact from delayed treatment.	14,413 patients (6 studies)	⊕⊖⊖⊖ VERY LOW ¹	Important

^a: GRADE Working Group grades of evidence (Guyatt et al. 2013).

⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.

⊕⊕⊕⊖ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

⊕⊕⊖⊖ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

⊕⊖⊖⊖ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

¹: Indirectness was rated serious: this was due to the delay in the included studies being shorter than what would likely be experienced by patients in our population.

²: Noting the small number of included studies; however both studies had >300 patients.

³: Noting the small number of included studies; however median sample size was >300 patients.

Overall survival was reported by five studies (Andrews et al. 2005; Dong et al. 2016; Korets et al. 2012; Redaniel et al. 2013; Sun et al. 2012), no statistical difference between patients with delayed treatment to immediate treatment were observed (delay was a median of three months in four studies and up to 24 months in Dong et al. (2016).

Cancer specific survival was reported by two studies (Andrews et al. 2005; Loeb et al. 2016), neither of which reported any difference in survival between groups. Andrews et al. (2005) compared patients receiving treatment less than 3.1 months following diagnosis to those receiving treatment more than 3.1 months post diagnosis. Loeb et al. (2016) compared delay lengths of less than 12 months, 12-24 months and greater than 24 months.

The proportion of patients with metastases formation was reported by four studies (Andrews et al. 2005; Dong et al. 2016; O'Brien et al. 2011; Warlick et al. 2006). Delayed treatment was not observed to have any impact on the rates of metastatic disease in any study.

Biochemical recurrence post treatment was reported by 14 studies (Abern et al. 2013; Andrews et al. 2005; Boorjian et al. 2005; Dong et al. 2016; Graefen et al. 2005; Khan et al. 2004; Korets et al. 2012; Kwan et al. 2006; Nam et al. 2003; Nguyen et al. 2005; O'Brien et al. 2011; Phillips et al. 2007; van den Bergh et al. 2010; Vickers et al. 2006). Abern et al. (2013) found men with intermediate risk disease had higher rates of recurrence when treatment was delayed more than nine months compared to patients receiving treatment within nine months. Nguyen et al. (2005) reported higher

rates of recurrence in men with high risk disease with treatment delays greater than three months compared to less than three months (55% versus 39%, $p=0.014$). O'Brien (2011) reported 12 per cent recurrence in patients with a treatment delay greater than six months compared to five per cent recurrence in those treated within six months. The remaining eleven studies reported that delayed treatment did not impact recurrence rates.

Seven studies reported no difference in rates of extra-capsular extension between patients receiving immediate treatment compared to those receiving delayed treatment (Abern et al. 2013; Dall'Era et al. 2012; Holmstrom et al. 2010; Korets et al. 2012; Loeb et al. 2016; O'Brien et al. 2011; van den Bergh et al. 2010). Three studies also reported no difference in rates of lymph node involvement (Khan et al. 2004; Korets et al. 2012; O'Brien et al. 2011). Rate of positive surgical margins were not observed to be impacted by delayed treatment in six studies (Abern et al. 2013; Dall'Era et al. 2012; Holmstrom et al. 2010; Lee et al. 2006; Loeb et al. 2016; O'Brien et al. 2011).

Rates of Gleason upgrade were reported by 10 studies (Abern et al. 2013; Dall'Era et al. 2012; Eroglu et al. 2014; Holmstrom et al. 2010; Korets et al. 2012; Loeb et al. 2016; O'Brien et al. 2011; O'Kelly et al. 2013; Sun et al. 2012; van den Bergh et al. 2010), five of which reported that delayed treatment was associated with higher rates of Gleason upgrade. However, Gleason upgrade does not necessarily indicate worse patient outcomes; consequently this outcome has a low importance and was not included in the summary of findings (Table 29).

Overall, evidence is mixed as to whether patients with intermediate or high risk disease will have their health compromised by a delay in treatment; however, most studies reported delay did not impact patient outcomes for patient with disease of any risk level.

B6 IMPACT OF REPEAT TESTING/MONITORING

This section details the use of mpMRI in patients diagnosed with low or intermediate risk PCa undertaking AS (Population 2).

No direct evidence was identified for Population 2; therefore linked evidence approach was taken.

B6.1 REFERENCE STANDARD

This is as discussed in Subsection B3.1.

B6.2 LITERATURE SOURCES AND SEARCH STRATEGIES: DIAGNOSTIC ACCURACY (POPULATION 2)

The search strategy used to identify diagnostic accuracy studies is described in Subsection B1.1.

B6.2.1 RESULTS OF LITERATURE SEARCH: DIAGNOSTIC ACCURACY (POPULATION 2)

The PRISMA flowchart at Figure 5, Subsection B1.1 provides a graphic depiction of the results of the literature search and the application of the study selection criteria as listed in Box 4 (Subsection A9).

An overview of the studies used to inform the assessment of Population 2 is given in Table 30. A profile of each included study is given in Appendix C.

Those studies which technically met the inclusion criteria, but which were excluded from the results section or meta-analyses, are listed in Appendix E. The risk of bias associated with these studies is discussed in Subsection B6.3 and the characteristics of the included studies are discussed in Subsection B6.4.

A total of 16 primary studies including 1,367 patients that assessed the diagnostic accuracy of mpMRI against prostate biopsy in patients on, or eligible for, AS programs were identified (Table 30) (Abd-Alazeez et al. 2014a; Almeida et al. 2016; Bonekamp et al. 2013; de Cobelli et al. 2015; Felker et al. 2016; Flavell et al. 2014; Margel et al. 2012; Mullins et al. 2013; Porpiglia et al. 2015; Recabal et al. 2016; Sahibzada et al. 2016; Siddiqui et al. 2015; Stamatakis et al. 2013; Vos et al. 2016; Walton Diaz et al. 2015; Wysock et al. 2016). As described in Subsections B3.2 and B3.4, only studies which reported the use of a PI-RADS ≥ 4 threshold were included in the meta-analyses (results from studies using a different threshold are presented in Appendix G). Considering only studies using the PI-RADS ≥ 4 threshold, six studies including 823 patients were identified for Population 2 (Abd-Alazeez et al. 2014a; Almeida et al. 2016; de Cobelli et al. 2015; Flavell et al. 2014; Porpiglia et al. 2015; Recabal et al. 2016).

Table 30 Key features of the included evidence comparing mpMRI against prostate biopsy in Population 2

Trial/Study	n	Level of evidence ^a	Risk of bias ^b	Key outcome(s) ^c	Result used in meta-analysis ^d
Abd-Alazeez et al. (2014)	137	III-2	High	TP, TN, FP, FN	Used
Almeida et al. (2016)	73	III-2	High	TP, TN, FP, FN	Used
Bonekamp et al. (2013)	50	III-2	High	TP, TN, FP, FN	Not used, other threshold
de Cobelli et al. 2015	223	III-2	Unclear	TP, TN, FP, FN	Used
Felker et al. (2016)	49	III-2	High	TP, TN, FP, FN	Not used, other threshold
Flavell et al. (2014)	64	III-2	High	TP, TN, FP, FN	Used
Margel et al. (2012)	60	III-2	High	TP, TN, FP, FN	Not used, other threshold
Mullins et al. 2013	37	III-2	High	TP, TN, FP, FN	Not used, per-patient data not available
Porpiglia et al. (2015)	120	III-2	Unclear	TP, TN, FP, FN	Used
Rebcal et al. (2016)	206	III-2	High	TP, TN, FP, FN	Used
Sahibzada et al. 2016	100	III-2	Unclear	TP, TN, FP, FN	Not used, per-patient data not available
Siddiqui et al. 2015	60	III-2	Unclear		Not used, diagnostic accuracy data not extractable
Stamatakis et al. (2013)	85	III-2	High	TP, TN, FP, FN	Not used, other threshold
Vos et al. 2016	24	III-2	High	TP, TN, FP, FN	Not used, PI-RADS ≥ 3
Walton Diaz et al. (2015)	58	III-2	High	TP, TN, FP, FN	Not used, other threshold
Wysock et al. (2016)	21	III-2	Unclear	TN, FN	Not used, bivariate data not available

^a: I=systematic review of level II studies; II=a study of test accuracy with an independent, blinded comparison with a valid reference standard, among consecutive patients with a defined clinical presentation;III-1=at study of test accuracy with an independent blinded comparison with a valid reference standard, among non-consecutive persons with a defined clinical presentation;III-2=a comparison with reference standard that does not meet the criteria for level II and III-1 evidence;III-3=diagnostic case-control study; IV=study of diagnostic yield (no reference standard).

^b: If any domain in the QUADAS-II assessment of risk of bias was rated as high then the overall assessment was high. If no domain was judged to have a high risk of bias but any domain was rated unclear then the overall assessment was rated as unclear. An overall rating of low was only given to studies where every domain had a low risk of bias. The breakdown of risk of bias by domain is provided in Subsection B3.3.

^c: Only TP, TN, FP and FN data were extracted from the primary studies, where sensitivity and specificity data only were reported then this was used to calculate TP, TN, FP and FN data.

^d: Only studies that reported bivariate diagnostic accuracy outcomes on a per-patient basis that used a PI-RADS ≥ 4 threshold were included. Some studies used a ≥ 3 PI-RADS threshold, these are presented separately in Appendix G. Other threshold refers to studies that did not report what threshold they used or that used a system other than PI-RADS to analyse the mpMRI images. These are also presented in Appendix G.

TP = true positive, FP = false positive, TN = true negative, FN = false negative, PI-RADS = Prostate Imaging Reporting and Data System.

B6.3 RISK OF BIAS ASSESSMENT: DIAGNOSTIC ACCURACY (POPULATION 2)

Risk of bias of the identified diagnostic accuracy studies was determined using a modified version of the QUADAS-2 quality appraisal tool (Whiting et al. 2011). The QUADAS-2 quality appraisal tool, with triggering questions and the criteria used to apply the tool is outlined in Appendix F, while the results are summarised in Table 85 (Appendix F). Quality appraisal was performed by one researcher and checked by a second. Any disagreement was resolved by consensus agreement with a third researcher.

Risk of bias was assessed in four domains: patient selection, index test, reference standard, and flow and timing. No studies were excluded due to an inappropriate risk of bias.

In the 'patient selection' domain five studies were found to have a low risk of bias. Eleven studies were assessed to have an unclear risk of bias due to a failure to report whether patient enrolment was consecutive (nine studies) or a failure to adequately report inclusion and exclusion criteria (two studies).

In the 'index test' domain nine studies were found to have a low risk of bias. Three studies (Flavell et al. 2014; Mullins et al. 2013; Stamatakis et al. 2013) were judged to have a high risk of bias for failing to determine the threshold for a positive test *a priori*. Four studies were assessed to have an unclear risk of bias due to a failure to report whether the mpMRI results were interpreted without knowledge of the biopsy results (three studies) and/or whether the threshold for a positive result was determined *a priori* (two studies).

In the 'reference standard' domain risk of bias was assessed to be low in two studies, high in seven studies due to a lack of blinding to the results of the index test and unclear in seven studies due to inexplicit reporting of whether the results of the reference test were interpreted without knowledge of the index test. All studies used a reference standard that was likely to classify to the condition correctly; pathology from biopsy specimens was used in all studies.

In the 'flow and timing' domain one study (Porpiglia et al. 2015) was assessed as having a low risk of bias. Six studies were assessed to have a high risk. This was due to the reference standard being performed more than three months after the mpMRI images were obtained in some or all included patients in four studies. In addition, Abd-Alazeez et al. (2014), Margel et al. (2012) and Vos et al. (2016) did not report results for all patients. Nine studies did not report the timing of the reference standard in relation to the index test and were therefore judged to have an unclear risk of bias in this domain.

There was no applicability issue identified relating to patient selection in any of the included studies. Nine studies were assessed as having applicability issues relating to the index test, of these none used a PI-RADS ≥ 4 cut-off as a positive result. This applicability issue was judged to be serious as the threshold used in a diagnostic accuracy study will have a large impact on the sensitivity and

specificity results. Due to this, studies with an applicability issue were not included in the meta-analysis of results; however, results from these studies are reported separately in Appendix G. Three studies were assessed to have a potential applicability issue with respect to the reference standard. Almeida et al. (2016), de Cobelli et al. (2015) and Porpiglia et al. (2015) used prostatectomy, rather than biopsy, as the reference standard. The impact of the differing reference standards was investigated using a subgroup analysis.

B6.4 CHARACTERISTICS OF THE EVIDENCE BASE: DIAGNOSTIC ACCURACY (POPULATION 2)

Appendix C contains tabulated details of the entire cohort of studies included in the evidence base for Population 2. Studies which did not have applicability issues with respect to patient selection and the index test are discussed in detail in this section of the report. These included studies that informed the estimates of sensitivity and specificity for the clinical utility and economics sections of the Assessment. These studies are referred to as ‘key studies’ (Abd-Alazeez et al. 2014a; Almeida et al. 2016; de Cobelli et al. 2015; Flavell et al. 2014; Porpiglia et al. 2015; Recabal et al. 2016).

Selected characteristics of the key studies for Population 2 are presented in Table 31.

Studies that included patients on AS programs were included. Studies where all patients were eligible for AS but elected to have prostatectomy were also included.

All included patients had tumours with a Gleason score less than or equal to six. Mean patient age in the key studies ranged from 59 to 63 years, while median age ranged from 60 to 66 years. This is consistent with data from the Victorian Prostate Cancer Registry which reported a median age of 66 years for patients enrolled in AS. Mean PSA ranged from 4.8 to 6.5ng/ml while median PSA ranged from 4.8 to 5.4ng/ml. This is in line with data from the Victorian Prostate Cancer registry that reported 100 per cent of men with low risk disease and 54 per cent of men with intermediate risk disease enrolled in AS had a PSA less than 10ng/ml (Victorian Prostate Cancer Clinical Registry Steering Committee 2015). Overall the included population of the key studies was judged to be consistent with the proposed population (Population 2) in the Protocol.

The included studies used 1.5 or 3.0T MRI, consistent with current clinical practice in Australia. All of the studies bar Flavell et al. (2014) performed T2, DW and DCE imaging. Flavell et al. (2014) did not obtain DCE images. Three of the studies used prostatectomy as the reference standard while three studies used TRUSGB with cognitive-MRI targeted cores. Due to the imperfect nature of biopsy as a reference standard, subgroup analysis by type of reference was performed to assess whether this had any impact on the estimates of the sensitivity and specificity of mpMRI.

Table 31 Selected characteristics of the key diagnostic accuracy studies for Population 2

Trial/Study Country Prospective or retrospective?	Number of patients Age (years)	Gleason score PSA level (ng/ml) PSA density (ng/ml²)	MRI details: T Coil Contrast	Reference standard details
Abd-Alazeez et al. (2014) UK Prospective	n=137 MRI +: mean 62.7 (SD 5.8) MRI EQ: 61.5 (SD 5.7) MRI -: 59.4 (SD 8.2)	Gleason ≤6 MRI+: median 7 (range 2-29) MRIEQ: median 8.3 (range 2.3-17) MRI-: median 5 (range 2.8-15) Density NR	1.5 or 3.0 T PPAC Gadoterate meglumine	TRUS + C-MRIGB 20 cores + targeted cores
Almeida et al. (2016) Italy Prospective	n=73 mean 63.0 (SD 5.85)	Gleason ≤6 Mean 6.03 (SD 1.93) Mean 0.14 (SD 0.05)	1.5T PPAC Gadopentetate dimeglumine	Prostatectomy
de Cobelli et al. (2015) Italy Retrospective	n=223 mean 62.75 (SD 8.28)	Gleason ≤6 Mean 6.02 (SD 1.91) Mean 0.13 (SD 0.04)	1.5T PPAC + ERC Gadobutrol	Prostatectomy
Flavell et al. (2014) USA Retrospective	n=64 median 60.7 (range 45.1-74.5)	Gleason=6 Mean 4.7 (range 0.6-9.7) NR	1.5 or 3.0T PPAC + ERC NA	TRUS + C-MRIGB 12-14 cores + targeted cores
Porpiglia et al. (2015) Italy Retrospective	n=120 median 65.0 (range 57-70)	Gleason ≤6 MRI+: Median 7.0 (IQR 6.39-10.1) MRI-: median 5.75 (IQR 4.88-9.22) MRI+: median 0.16 (IQR 0.15-0.24) MRI-: median 0.13 (IQR 0.11-0.21)	1.5T PPAC + ERC NR	Prostatectomy
Rebcal et al. 2016) USA Retrospective	N = 206 median 63 (IQR 57-68)	Gleason ≤6 Median 5.2 (IQR 3.8-7.4) Median 0.13 (IQR 0.08-0.19)	1.5 or 3.0T PPAC +/- ERC NR	TRUS + C-MRIGB 14 cores + targeted cores

^a: Only patients who received a 1.5T MRI were imaged using an endorectal coil.

PPAC = pelvic phased array coil, ERC = endorectal coil, MRI = magnetic resonance imaging, MRI+ = MRI positive, MRI- = MRI negative, MRIEQ = MRI equivocal, PSA = prostate specific antigen, TRUS = trans-rectal ultrasound, C-MRIGB = cognitive MRI guided biopsy, T = tesla, SD = standard deviation, IQR = inter quartile range.

B6.5 OUTCOME MEASURES AND ANALYSIS: DIAGNOSTIC ACCURACY (POPULATION 2)

To assess the diagnostic accuracy of the proposed test, studies were only included if they provided data that could be extracted into a classic 2 x 2 table, in which the results of the index test or the

comparator were cross-classified against the results of the reference standard⁵, and Bayes' Theorem was applied (Table 32):

Table 32 Diagnostic accuracy data extraction

-	-	Reference standard		-
-	-	<i>Disease +</i>	<i>Disease –</i>	-
Index test	<i>Test +</i>	true positive	false positive	Total test positive
Or comparator	<i>Test –</i>	false negative	true negative	Total test negative
-	-	Total with disease	Total without disease	-

The primary outcome reported by all of the key studies, was the ability of mpMRI to detect any upgrade in cancer in patients eligible for AS for previously diagnosed PCa.

Only studies that provided per-patient data were included in the meta-analysis as the decision whether to perform a biopsy is made on a per-patient basis in the clinical algorithm. No key study was excluded from the meta-analysis on this basis.

The bivariate model and hierarchical summary receiver operating characteristic (HSROC) analyses were conducted for Population 2. The mixed modelling approach described by Reitsma et al. (2005) was used to provide estimated summaries of sensitivity and specificity and the corresponding 95 per cent confidence ellipses (Reitsma et al. 2005). The HSROC curve described by Rutter and Gatsonis was generated and the associated area under the curve (AUC) was compared across imaging techniques (Rutter and Gatsonis 2001). Heterogeneity was estimated using visual inspection of the prediction interval.

A priori, it was determined that the type of reference standard would be investigated by subgroup analyses. No other subgroup analyses were intended to be performed due to the small number of key studies identified for Population 2. No *post-hoc* subgroup analyses were performed.

Estimates of sensitivity and specificity were performed for the detection of any cancer upgrade as defined in Table 33.

Meta-analyses were conducted in R i386 v 3.1.2 using the “mada” package (Doebler and Holling 2012). Publication bias was not assessed due to the inherent difficulty in estimating publication bias for diagnostic studies and inaccuracy in interpretation of results (Macaskill et al. 2010).

⁵ Armitage, P, Berry, G & Matthews, JNS 2002, *Statistical methods in medical research*, fourth edn, Blackwell Science, Oxford.

B6.6 RESULTS OF THE SYSTEMATIC LITERATURE REVIEW: DIAGNOSTIC ACCURACY (POPULATION 2)

IS MPMRI ACCURATE?

Summary – What is the diagnostic accuracy of mpMRI to detect upgrade cancer in patients on active surveillance?

Six studies, including 820 patients, were identified that reported a per-patient analysis of the diagnostic accuracy of mpMRI to detect upgraded cancer in patients on active surveillance programs. Pathology of samples obtained by biopsy was the reference standard in three studies, while three studies used pathology of prostatectomy specimens. There were no applicability issues identified between the included key studies and the proposed population in the Protocol. Only studies using the same threshold for PI-RADS scoring as that stated in the Protocol (\geq PI-RADS 4 for a positive result) were included in this analysis.

For the detection of cancer upgrade, mpMRI has a sensitivity of 79.3% (95% CI [74.6, 83.3]) and a specificity of 55.1% (95% CI [50.4, 59.8]) – results from meta-analysis of six studies including 820 patients).

The narrow 95% confidence and prediction regions reflects the high level of certainty in the point estimate and the low level of heterogeneity present in the evidence base. Subgroup analysis by type of reference standard did not reveal any statistical difference between studies using a biopsy reference standard and those using prostatectomy samples.

It is therefore suggested that the diagnostic accuracy of mpMRI for detected upgraded cancer in men on active surveillance is inferior to TRUSGB or TPUSGB. The quality of the diagnostic accuracy outcomes was rated good using the GRADE tool reflecting the consistent nature of the evidence base in this population.

Table 33 Results of key accuracy trials comparing mpMRI against biopsy

Study ID	Study characteristics	Result	Definition of upgraded cancer
Abd-Alazeez et al. (2014) UK	Prospective No ERC	Sensitivity=77% Specificity=56%	Gleason \geq 7
Almeida et al. (2016) Italy	Prospective No ERC	Sensitivity=76% Specificity=43%	Gleason \geq 7
de Cobelli et al. (2015) Italy	Retrospective ERC	Sensitivity=84% Specificity=52%	Gleason \geq 7
Flavell et al. (2014) USA	Retrospective ERC	Sensitivity=79% Specificity=58%	Gleason \geq 7
Porpiglia et al. (2015) Italy	Retrospective ERC	Sensitivity=73% Specificity=62%	Gleason \geq 7, extra capsular disease, index tumour volume \geq 1.3 cm ³ or total tumour volume \geq 2.5 cm ³
Rebcal et al. 2016) USA	Retrospective ERC	Sensitivity=82% Specificity=57%	Gleason \geq 7

ERC = endorectal coil.

Table 34 Summary of findings for the accuracy of mpMRI, relative to TRUSGB or TPUSGB for the detection of upgraded cancer in patients on active surveillance programs (assumed pre-test probability of 30%)

Outcomes	Intervention [95%CI]	Quality of evidence ^a	Importance
Sensitivity % [95% CI]	79.3 [74.6, 83.3]	⊕⊕⊕⊕ HIGH ¹	Critical
Specificity % [95% CI]	55.1 [50.4, 59.8]	⊕⊕⊕⊕ HIGH ¹	Critical
PPV % [95% CI]	59.4 [53.5, 65.0]	⊕⊕⊕⊕ HIGH ¹	Important
NPV % [95% CI]	76.2 [70.1, 81.4]	⊕⊕⊕⊕ HIGH ¹	Important

^a:GRADE Working Group grades of evidence (Guyatt et al. 2013).

⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.

⊕⊕⊕⊙ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

⊕⊕⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

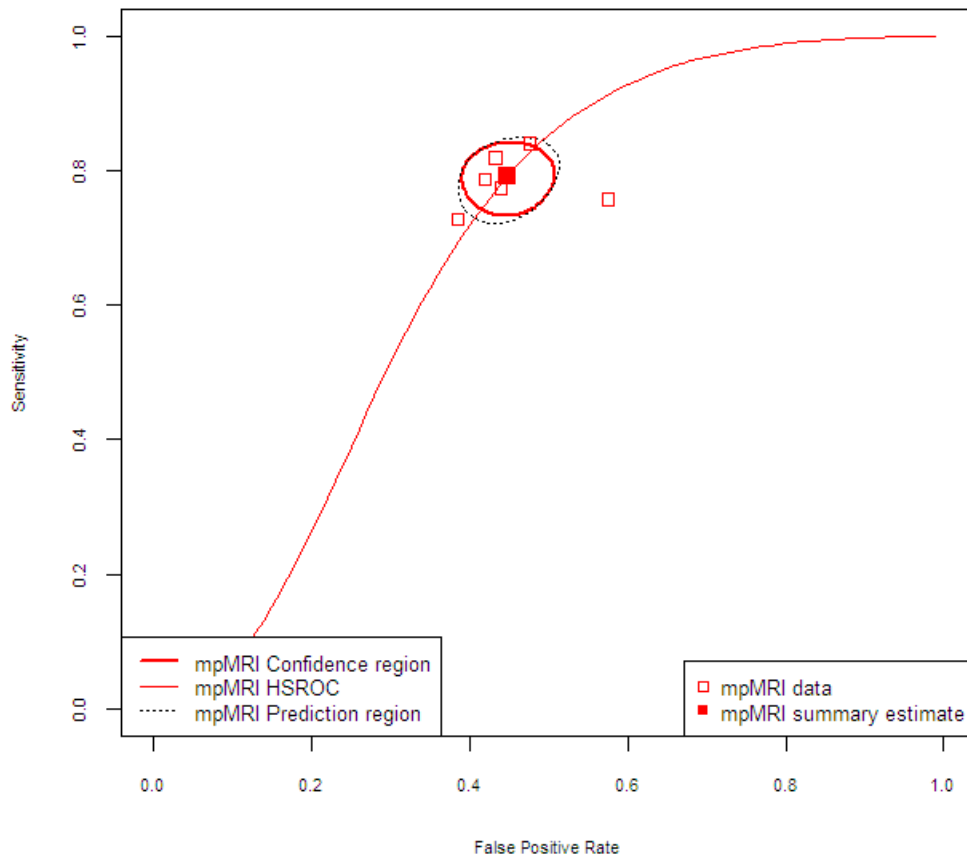
¹: While the confidence intervals indicated a high level of precision, the relatively moderate number of studies and the moderate median population size may warrant downgrade in imprecision.

CI = confidence interval, PPV = positive predictive value, NPV = negative predictive value.

For the detection of upgraded cancer in men enrolled in or eligible for AS programs, mpMRI was estimated to have a sensitivity of 79.3 per cent (95% CI [74.6, 83.3]) and a specificity of 55.1 per cent

(95% CI [50.4, 59.8]). The HSROC curve and summary estimate with 95 per cent confidence region and 95 per cent prediction region is provided in Figure 11.

Figure 11 HSROC curve and bivariate model results for the diagnosis of any cancer by mpMRI in Population 2.



The narrow confidence region reflects a high level of certainty in the point estimate. The prediction region almost overlaying the confidence region reflects the low level of heterogeneity present in the evidence base and reflects that future studies in this population will report results consistent with the results of this meta-analysis.

Subgroup analysis was undertaken to explore the impact of using a ‘perfect’ reference standard (prostatectomy) compared to an imperfect reference standard (biopsy) (Table 35). No statistical difference was found between the two groups. The inclusion of studies using prostatectomy as a reference standard did not change the outcomes of the meta-analysis; therefore, the overall results were used to inform this Assessment.

Table 35 Subgroup analysis for the use of mpMRI to monitor patients in Population 2

Subgroup	Patients/studies	Sensitivity (%) [95% CI]	Specificity (%) [95% CI]
All studies	820 patients (6 studies).	79.3 [74.6, 83.3]	55.1 [50.4, 59.8]
Prostatectomy reference standard	413 patients (3 studies).	79.0 [70.4, 85.6]	53.7 [44.9, 62.2]
Biopsy reference standard	407 patients (3 studies).	79.6 [72.7, 85.0] 0.796 [0.727, 0.850]	56.7 [50.3, 62.8]

CI = confidence interval.

B6.7 EXTENDED ASSESSMENT OF RELIABILITY EVIDENCE (POPULATION 2)

An assessment of the reliability of mpMRI using PI-RADS can be found in Subsection B3.7 of this report. No key study for Population 2 reported any additional inter-reader agreement data than that reported in B3.7.

B6.8 ASSESSMENT OF CLINICAL UTILITY (POPULATION 2)

Summary – Does imaging with mpMRI improve health outcomes for men suspected of having prostate cancer?

Low-concern patients: advice from the Applicant is that 30-35% of patients will have their disease upgraded while on active surveillance.

mpMRI True positive: No evidence that patients with a true positive will experience any change in management or change to health outcomes was identified.

mpMRI False positive: No evidence that patients with a false positive will experience any change in management or change to health outcomes was identified.

mpMRI True negative: These patients will avoid having a biopsy and therefore avoid the adverse events associated with biopsy. The adverse events are discussed in Subsection B7.

mpMRI False negative: limited evidence from a single study with a moderate risk of bias suggests delayed treatment following upgrade of disease is not associated with increased rates of positive surgical margins.

High concern patients: all high-concern patients will undergo a biopsy. No evidence that patients who undergo a biopsy of any type will experience any change in management or change to health outcomes was identified.

Summary: there is only limited, low quality evidence to support any comparison between mpMRI and TRUSGB/TPUSGB with regards to any change in patient outcomes that would be associated with the introduction of mpMRI in this population.

For men with a low-risk tumour who experience a disease progression while on AS treatment decisions are made on the basis of biopsy results. Under the proposed management algorithms, mpMRI results will be used to decide if patients should receive a biopsy. For men with suspected PCa, a PI-RADS score ≤ 3 will result in low-concern patients avoiding a biopsy; the therapeutic effect of this biopsy avoidance is discussed in Subsection B5.2. High-concern men with a PI-RADS score ≤ 3 will receive a systematic biopsy under current and proposed management algorithms.

Patients who receive a PI-RADS score of 4 or 5 will have a change in the type of biopsy they receive (change from TRUSGB or TPUSGB to MRIGB). Any change in management associated with this change in biopsy is the subject of Application CA 1424. The Assessment Group for Application CA 1424 has advised that no studies investigating the change in management associated with US versus MRI guided biopsies was identified. In addition, the Assessment group for CA 1424 has advised that no peer-reviewed literature has been identified investigating safety differences between biopsy guidance techniques. Similarly, our own searches into the safety of prostate biopsy (Subsection B7) have not identified any literature on this topic. There is no evidence that safety outcomes are different for trans-rectal biopsy performed under US or MRI guidance.

As described in Subsection B5.1, results from Schoots et al. (2015) show no difference in accuracy associated with biopsy type; therefore, there is unlikely to be any difference in management for patients receiving a biopsy.

Low-concern patients: advice from the Applicant is that between 30 and 35 per cent of patients will have their disease upgraded while on AS.

mpMRI True positive: These patients have PCa and will receive a biopsy to guide the treatment decision under current management these patients will receive a TRUSG or TPUSGB. Under the proposed algorithm these patients will receive MRIGB. Using the approach recommended by Merlin and Leman (Merlin et al. 2013), no investigation of therapeutic effectiveness has been undertaken for these patients as treatment for these men is unlikely to change under the proposed algorithm owing to the equivalent accuracy of the various biopsy types. Current treatment option for patients following biopsy may include further AS, radical prostatectomy, radiation therapy, androgen deprivation therapy, brachytherapy, high intensity focused US and/or chemotherapy (Evans et al. 2013).

mpMRI False positive: These patients do not have PCa but have been incorrectly identified as by mpMRI. Under current management these patients will receive a TRUSGB or TPUSGB. Under the proposed management these patients will receive MRIGB. It is expected that biopsy of any type will correct the misdiagnosis by mpMRI and these patients will not receive unnecessary treatment.

mpMRI True negative: These patients do not have PCa and have been accurately diagnosed by mpMRI. These patients will avoid having a biopsy and therefore avoid the adverse events associated with biopsy. The adverse events are discussed in Subsection B7.

mpMRI False negative: These patients have PCa but have been incorrectly diagnosed as cancer free by mpMRI. These patients will avoid the adverse events associated with biopsy as described in Subsection B7. However, the patients will be subject to a delay in the diagnosis of their disease. According to the clinical algorithm for the proposed service, these patients will be re-evaluated with a PSA test (three to four months) and with a DRE (six to twelve months) after the negative mpMRI. Results from these follow-ups will determine whether an additional mpMRI scan is required, otherwise, patients receive a scan every three years. The impact of delayed treatment for this group of patients has been investigated in a systematic literature review (described below).

High-concern patients: As all high-concern patients will receive a biopsy, regardless of the results of the mpMRI, no change in management and no changes to therapeutic effectiveness are expected for this population. The basis for this is the same as was discussed for high-concern patients in Population 1 (Subsection B5).

No studies were identified that measured the change in management in Population 2.

The impact of delayed treatment in low-concern patients with a false negative mpMRI result was assessed in a systematic literature review. The details of this review are described in Subsection B5.2.1.

One study was identified that assessed the impact of a delay between cancer upstaging and treatment (Hussein et al. 2015).

Hussein et al. (2015) included 219 men who were upgraded from Gleason 6 to Gleason ≥ 7 . The median time between upgrading and treatment was 28 months (IQR 16-52) and the median length of follow-up was 59 months (IQR 37-89). A delay before treatment was not associated with an increase in the proportion of patients with positive surgical margins (OR 1.01 (95% CI [0.97, 1.05], $p = 0.62$).

B6.9 INTERPRETATION OF EVIDENCE ON MONITORING (POPULATION 2)

Six studies were identified that reported a per-patient analysis of the diagnostic accuracy of mpMRI to detect upgraded cancer in patients on AS programs. Pathology of samples obtained by biopsy was the reference standard in three studies, while three studies used pathology of prostatectomy specimens. There were no applicability issues identified between the included key studies and the proposed population in the Protocol.

For the detection of cancer upgrade, mpMRI has a sensitivity of 79.3 per cent (95% CI [74.6, 83.3]) and a specificity of 55.1 per cent (95% CI [50.4, 59.8]) – results from meta-analysis of six studies including 820 patients.

The narrow 95 per cent confidence and prediction regions reflects the high level of certainty in the point estimate and the low level of heterogeneity present in the evidence base. Subgroup analysis by type of reference standard did not find any statistical difference between studies using a biopsy reference standard and those using prostatectomy samples.

No study reported any data on the reliability of mpMRI for monitoring patients on AS.

The only change in management associated with the introduction of mpMRI for Population 2 is the avoidance of biopsy by low-concern patients who have a negative mpMRI result. Patients for whom this is a true negative will avoid the adverse events of biopsy. Patients for whom this is a false negative will avoid the adverse events of biopsy at the expense of delayed treatment. A single study with moderate risk of bias found delayed treatment was not associated with increased rates of positive surgical margins; however, more research is required to confirm this result and to look at other outcomes, for example patient survival and other clinically relevant measures such as rates of metastatic disease, extra-capsular extension and lymph node involvement.

Despite the inferior diagnostic accuracy of mpMRI compared to TRUSGB or TPUSGB the limited evidence suggests that any delay in treatment will not impact patients overall outcomes. Therefore a conservative approach has been taken and mpMRI is considered non-inferior compared to current management for patients in Population 2.

B7 EXTENDED ASSESSMENT OF COMPARATIVE HARMS

B7.1 SAFETY OF MPMRI

None of the diagnostic accuracy studies reported on safety outcomes associated with mpMRI. While MRI is considered safe for most patients, there are some potential adverse events associated with the use of magnetic fields and contrast agents which are outlined in this section. The following presents safety information for MRI when used in the general population.

THE STATIC MAGNETIC FIELD

Safety issues to consider with strong static fields are interaction with implantable medical devices, fringe fields, biological effects, attractive force causing projectile hazards, and interaction with other equipment (Schenck 2001a; Schenck 2001b).

The strong magnetic field can affect implantable medical devices in exposed people. Any ferromagnetic component of an implantable device may experience both an attractive and a torque force. Implantable medical devices can be pacemakers, prostheses, clips, stents and neuro-stimulators. It is important to check the MRI compatibility of an implantable medical device.

Acute cardiac effects have been occasionally observed in relation to short-term exposure to static magnetic fields above 8T (World Health Organization 2006). However, acute exposure to static magnetic fields up to 8T is unlikely to have any adverse effect on health (ICNIRP 2004; National Radiological Protection Board 1991).

TIME-VARYING MAGNETIC FIELD

In MRI, three orthogonal magnetic field gradients are switched on and off to select the region of diagnostic interest and to spatially encode the MRI signals. The faster the sequence, the greater the rate of change of the gradient fields used and the current density induced in the tissue. The safety concerns with the time-varying magnetic field gradients are biological effects, including peripheral nerve stimulation, muscle stimulation (Kangarlu A and Robitaille PML 2000) and acoustic noise (Price DL et al. 2001; RANZCR 2007). In most cases any discomfort can be managed.

RADIOFREQUENCY MAGNETIC FIELDS

The main safety issues for radiofrequency (RF) fields used in MRI are thermal heating leading to heat stress induced current burns and contact burns.

Heat stress is of particular concern for some patients, such as those suffering from hypertension or those on drugs such as diuretics or vasodilators. Cardiovascular strain is an issue resulting from

thermoregulatory responses to body temperatures raised over a short period of time by more than 0.5°C in vulnerable people (Shellock FG 2001).

OTHER CONSIDERATIONS

Claustrophobia can inhibit some patients from undergoing MRI scans. Sedation and general anaesthetic are possible solutions for these patients, as well as non-pharmaceutical management which may include education or continuous verbal contact with patient (Thorpe et al. 2008).

Other patients at increased risk of harm from MRI are those with a previous reaction to gadolinium chelate (discussed below), other allergies, asthma, and patients with end-stage renal failure (ICNIRP 2004). These patients may be imaged without the use of contrast agent or an alternative form of imaging such as CT or X-ray may be used.

SAFETY OF GADOLINIUM-BASED CONTRAST AGENTS

mpMRI currently involves a sequence of contrast-enhanced imaging, requiring a compound for contrast enhancement. The most commonly used contrast agents are gadolinium-based. Eleven studies reported on the safety of gadolinium contrast agents (Bluemke et al. 2005; Davenport et al. 2014; Davenport et al. 2013; Endrikat et al. 2015; Gschwend et al. 2011; Hamm et al. 1995; Huppertz et al. 2004; Ichikawa et al. 2010; Raman et al. 2010; Reimer et al. 1996; Zeng et al. 2013). The most frequent adverse events resulting from the use of gadolinium-based contrast agents include:

- dyspnoea (11%)
- nausea (1%)
- headache (1%)
- injection site pain/reaction/bruise (1%)
- taste perversion (1%)
- flushing (0.7%)
- olfactory dysfunction (0.7%)
- back pain (0.6%)
- dizziness (0.5%)
- vasodilation (0.5%)
- rash (0.4%).

Other adverse events occurring less than 0.1 per cent of patients were an increase in blood pressure, blood component change, diarrhoea, dry mouth, bundle branch block, sweating, palpitation, injection site bruise, akathisia, paraesthesia, hypotension and anaemia. All of the adverse events are expected to be transient, and only one of the contrast-related adverse events is considered potentially serious (dyspnoea). The rate of severe respiratory motion artefact related to dyspnoea was significantly correlated in the literature to a high (20 ml) dose of gadoxetic acid, which is more than would reasonably be used (10 ml) (Davenport et al. 2014).

Overall, it appears gadolinium-based contrast agents for MRI are generally safe to use in most patients.

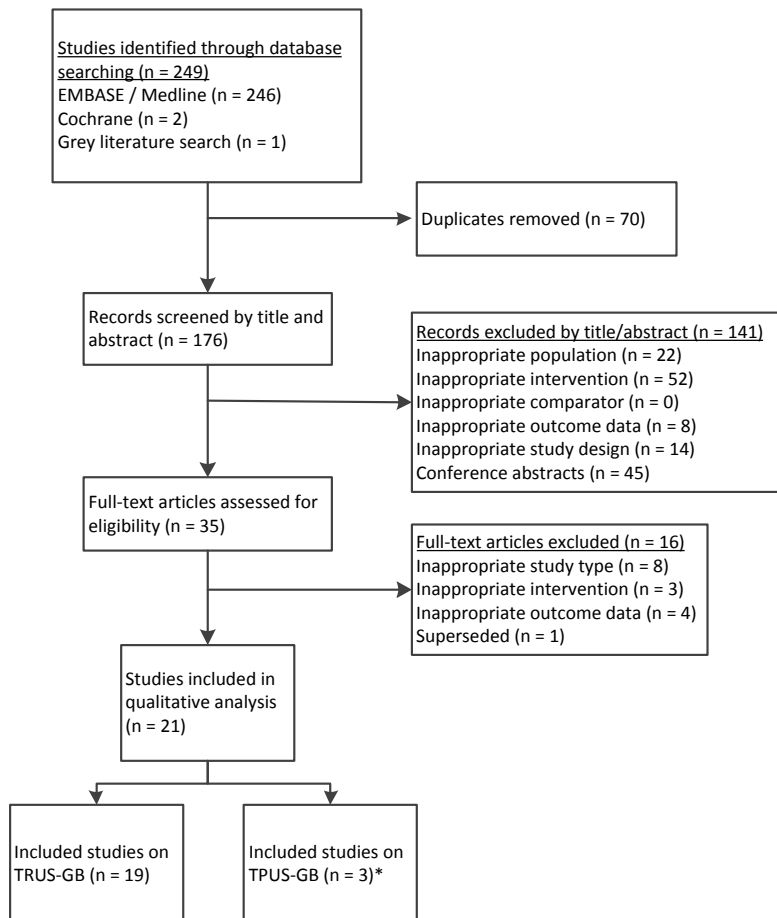
SUMMARY

The most relevant safety issues associated with MRI are the risks associated with internal ferromagnetic objects, and heat stress (particularly in patients with hypertension or taking diuretics or vasodilators). There is a potential risk of contact burns if patient positioning is inappropriate. Additionally, claustrophobia may prevent some patients from undergoing MRI scans. There are limited adverse events associated with gadolinium-based contrast agents. While it is recognised that there are also potential risks associated with the use of strong magnetic fields, these are unlikely to occur and are associated with higher field strengths than those used in clinical practice. MRI is an established technique and is considered safe for almost all patients.

B7.2 SAFETY OF COMPARATOR TEST – BIOPSY

A systematic search was conducted on safety issues related to prostate biopsy. The search criteria included primary studies or systematic reviews reporting the safety of TRUSGB or TPUSGB. The PRISMA flowchart in Figure 12 provides a graphic depiction of the results of the literature search.

Figure 12 Study selection process for studies assessing the safety of biopsy



*Loeb et al. (2013) evidence for both groups

B7.2.1 RISK OF BIAS: SAFETY OF COMPARATORS

The risk of bias in all studies used in the safety section was assessed using an appropriate tool for each study type.

Systematic review

The two included reviews (Chang et al. 2013; Loeb et al. 2013) were appraised using the AMSTAR tool (Shea et al. 2007) (Table 86, Appendix F). Chang et al. (2013) did not report any methods and so was considered a narrative review. Loeb et al. (2013) was appraised as a systematic review. An *a priori* design was provided and a comprehensive literature search conducted. It is unclear how many researchers selected and extracted the studies. The characteristics of included studies were provided; however, the quality assessment of studies was not documented. Studies were reported narratively which is appropriate for a quantitative systematic review, it is unclear whether the quality of the studies was used in formulating conclusions. Both studies were considered to be of moderate risk of bias.

Randomised controlled trial

The single included RCT was appraised using the Cochrane Collaboration's tool for assessing risk of bias in randomised trials (Higgins et al. 2011). The method of randomization was not described with simply the word 'random' used. The study was reported as 'single blind', implying investigators, but not the study patients, knew which treatment was allocated. The blinding status of outcome assessors was not reported. Despite this, the article did provide adequate information about the study and the reporting issues were not considered to impact this assessment (Table 87, Appendix F).

Comparative studies

Eight comparative studies which did not reach the standard of RCT were appraised using the Downs and Black checklist for non-randomized studies (Downs and Black 1998). Most studies failed to describe patients lost to follow-up; did not report on "data dredging" and failed to conceal treatment allocation. Study subjects were assigned to intervention groups in one study (Marino et al. 2015), in the other studies groups were decided by what treatment patients had received. Although the database studies had a powerful number of patients, no studies calculated the number of patients *a priori* to allow for effect size. For all but one study, in which patients were taking aspirin for heart disease (Kariotis et al. 2010), it appears patients represent the population from which they were recruited. It cannot be known if those who did not consent were different from those who did, as it is unclear if any men asked did not consent to participate. The studies were considered to be at moderate risk of bias (Table 88, Appendix F).

Case series

Ten case series were appraised using a modified version of the Downs and Black tool (Moga C et al. 2012). Half of the studies collected patient data in multiple centres. Less than half of the studies provided estimates of random variability in the data analysis of relevant outcomes. Three studies used self-report measures and six used clinical measures. Patients were reported to be recruited consecutively in one study. Loss to follow-up was reported in one study. No study measured outcomes before and after the intervention as this was not applicable in the case of post-biopsy complications. Across the studies competing interest and source of support were not consistently reported.

B7.3 HARMs ASSOCIATED WITH TRANS-RECTAL BIOPSY

The evidence base for trans-rectal prostate biopsy consists of nine case series (Level IV studies), six comparative studies with controls (Level III-2), one comparative study with historical control (Level III-3), two randomised controlled trials and one systematic review. A summary of findings is presented in Table 36. Full results are presented in Table 94 (Appendix H). No meta-analysis was

undertaken due to heterogeneity between studies in study designs and in reporting of adverse events. Results are described narratively by study size with large (greater than 5,000 patients) studies considered key evidence and moderate (1,000-5,000 patients) and smaller sized (greater than 1,000 patients) studies summarised aggregately.

Table 36 Summary of findings for the safety of trans-rectal and trans-perineal prostate biopsy

Outcomes	Patients/Studies	Impact	Quality of evidence ^a	Importance
Major infection follow-up median 1 month.	45,492 patients (8 studies).	Major infection ranged from 0.2 per cent to 2.4 per cent in the trans-rectal biopsy studies. There was no major infection reported in the trans-perineal biopsy studies.	⊕⊕⊖⊖ LOW	Critical
Minor infection follow-up median 1 month.	132,239 patients (9 studies).	Minor infection ranged from 0.0 per cent to 0.03 per cent in the trans-perineal biopsy studies and from 0.7 per cent to 6.9 per cent in the trans-rectal biopsy studies.	⊕⊕⊖⊖ LOW	Critical
Re-hospitalisation follow-up median 1 month.	292,956 patients (9 studies).	Re-hospitalisation ranged from 0.7 per cent to 2.1 per cent in the trans-perineal biopsy studies and from 0.4 per cent to 5.5 per cent in the trans-rectal biopsy studies.	⊕⊕⊖⊖ LOW	Critical
Bleeding related follow-up median 1 month.	334,688 patients (13 studies).	Bleeding ranged from 0.1 per cent to 6.1 per cent in the trans-perineal biopsy studies and from 0.8 per cent to 88.0 per cent in the trans-rectal biopsy studies.	⊕⊖⊖⊖ VERY LOW 1,2	Important
Urinary obstruction follow-up median 1 month.	132,020 patients (12 studies).	Urinary obstruction ranged from 0.4 per cent to 38.0 per cent in the trans-perineal biopsy studies and from 0.8 per cent to 21.0 per cent in the trans-rectal biopsy studies.	⊕⊖⊖⊖ VERY LOW 1	Important

^a: GRADE Working Group grades of evidence (Guyatt et al. 2013).

⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.

⊕⊕⊕⊖ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

⊕⊕⊖⊖ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

⊕⊖⊖⊖ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

B7.3.1 MORTALITY ASSOCIATED WITH TRANS-RECTAL BIOPSY

Although uncommon, death by sepsis can occur following prostate biopsy. There were two deaths reported in the literature from sepsis resulting from a trans-rectal biopsy-related infection. A single death due to sepsis was reported (Pinsky et al. 2014) in a two centre cohort study of 4,836 patients staged between 1993 and 2001. Details of attempts to reduce risk of infection were not reported in this study. Four patients died, three of non-biopsy related causes such as heart disease, and one of sepsis resulting from a trans-rectal biopsy-related infection, in a case series of 2,023 patients (Simsir et al. 2010) All patients underwent antibiotic prophylaxis and enema before biopsy.

B7.3.2 MORBIDITY ASSOCIATED WITH TRANS-RECTAL BIOPSY

Roth et al. (2015) reported a case series of 34,865 prostate biopsies performed in Victoria, Australia between 2001 and 2008 (Roth et al. 2015). Overall 3.7 per cent of patients were re-admitted to a Victorian hospital within seven days following a trans-rectal biopsy. Most significantly, 1.7 per cent of patients were re-admitted with biopsy-related infection; indicators of infection included sepsis, UTI, fever, acute prostatitis, and abscess of prostate. Causes of re-admissions not attributed to infectious complications included:

- bleeding (0.15%)
- urinary obstruction (0.1%)
- prostatitis (0.09%)
- haematuria (0.06%),
- other complications not resulting from prostate biopsy (0.1%).

The results suggest that infection following biopsy is an uncommon but clinically significant event in Australia.

Nam et al. (2013) reported on database study in Ontario, Canada. Of the 75,190 men who underwent biopsy in Ontario between 1996 and 2005, 1.4 per cent were readmitted to hospital within 30 days, with most readmissions occurring in the first week. Biopsy-related infection made up the majority of complications (0.7%), followed by bleeding (0.2%), and urinary obstruction (0.1%). It was reported that the rate of hospitalisation due to infection increased almost seven-fold over the study period from 0.03 per cent in 1996 to 0.2 per cent in 2005 (Nam et al. 2013).

Carignan et al. (2012) reported a case-control study in a single centre in Quebec Canada. Of the 5,798 prostate biopsies performed between 2002 and 2011, 0.8 per cent patients had biopsy-related infection. Overall, 0.5 per cent of patients needed to be hospitalised and 0.08 per cent were admitted to ICU. It was proposed that antibiotic resistance has contributed to increasing biopsy-related infection (Carignan et al. 2012).

Anastasiadis et al. (2015) reported on a registry study of all men undergoing biopsy in England between 2000 and 2008. From the 198,361 prostate biopsies performed, 3.7 per cent of patients had a complication warranting hospitalisation. These were made up of haematuria (1.4%), urinary obstruction (1.3%), and UTI/sepsis (1.1%). A 20 per cent increase in biopsy-related hospitalisation was found in the nine-year study period (Anastasiadis et al. 2015).

Five studies reporting trans-rectal biopsy-related complications had a sample size of 1,000 to 5,000 patients (Pinsky et al. 2014; Roberts et al. 2002; Rosario et al. 2012; Simsir et al. 2010; Zaytoun et al. 2011). In these studies minor infection ranged from 0.8-2.7 per cent, major infection 0.2-3.0 per cent, urinary obstruction 0.4-1.9 per cent, rectal bleeding 0.3-37 per cent, haematuria 4.4-12.1 per cent, haemospermia 0.5-0.8 per cent of patients. Pain (2%), UTI (1.3%), and bacteraemia (0.3%) were only reported in one study (Roberts et al. 2002). Results from Rosario et al. (2012) were removed from the data on rectal bleeding, haematuria, haemospermia, and pain ranges as the study used self-reporting, rather than hospital records to collect data on these outcomes. Hospitalisation was only reported in one study at 0.4 per cent (Roberts et al. 2002).

Nine studies reporting trans-rectal biopsy-related complications had a sample size of less than 1,000 patients (Helfand et al. 2013; Kariotis et al. 2010; Marino et al. 2015; Mohammed et al. 2016; Petteffi et al. 2002; Sahin et al. 2015; Solberg et al. 2011; Utrera et al. 2011a; Utrera et al. 2011b), and a further eleven like studies were extracted from a systematic review (Loeb et al. 2013). In these studies minor infection ranged from 5.5-6.9 per cent, major infection 0.6-2.4, UTI 1.5-30.0, urinary obstruction 0.9-24.1, rectal bleeding 0.7-51.0, haematuria 0.7-63.0, haemospermia 8.2-88.0, bacteraemia 0.4-4.5, fever 1.0-15.0 per cent of patients. Prostatitis (1.4%), pain (64%), and bacteriuria (4.5%) were only reported in one study each (Solberg et al. 2011; Utrera et al. 2011a; Utrera et al. 2011b). One primary study and one systematic review also reported on erectile dysfunction (Helfand et al. 2013; Loeb et al. 2013). Most studies measured erectile dysfunction with IIEF-5 and reported that one month after prostate biopsy mild to severe erectile dysfunction affected from 2.2-92.1 per cent of patients. It is not known what portion of these studies used self-reported outcomes. Hospitalisation ranged from 0.5 -5.5 per cent.

B7.4 HARMS ASSOCIATED WITH TRANS-PERINEAL BIOPSY

Three studies were identified that assessed the safety of trans-perineal biopsies. Results from these studies are reported in Table 95 (Appendix H); a summary of findings is reported in Table 36.

B7.4.1 MORTALITY ASSOCIATED WITH TRANS-PERINEAL BIOPSY

There is no evidence in the literature of deaths related to trans-perineal prostate biopsy.

B7.4.2 MORBIDITY ASSOCIATED WITH TRANS-PERINEAL BIOPSY

One primary study and two systematic reviews we identified with safety results for TPUSGB (Chang et al. 2013; Loeb et al. 2013; Mai et al. 2016). Hospitalisation after TPUSGB ranged from 0.7-2.1 per cent.

No meta-analysis was undertaken due to heterogeneity between studies in study designs and in reporting of adverse events. Results are described narratively by study size with large (greater than 3,000 patients) studies considered key evidence.

Mai et al. (2016) reported on a case series of 3,007 trans-perineal biopsies conducted in a Beijing hospital between 2003 and 2013. Overall, 2.1 per cent of patients had complications requiring hospitalisation or emergency care. Total rates of complications, including those not requiring hospitalisation, were major infection (0.03%), acute urinary obstruction (1.9%), urethral bleeding (0.1%), haematuria (47%), haemospermia (6.1%), and perineal haematoma (0.5%).

Two systematic reviews reporting trans-perineal biopsy-related complications from studies with a sample size of less than 1,000 patients (Chang et al. 2013; Loeb et al. 2013). Chang et al. (2013) included 34 studies with a total of 8,044 patients. Loeb et al. (2013) included 17 studies with a total of 3,203 patients. In the studies reported in these reviews, urinary obstruction ranged from 0.5-20.6 per cent, significant haematuria 0.3-57.0 per cent, mild/transient haematuria 3.7-45.3 per cent, UTI 1.1-8.9 per cent, and fever 0.5-5.3 per cent of patients. Significantly, the majority of studies in these reviews reported that no infection occurred in any patient. One study included in Loeb et al. (2013) with a sample size of 40 reported haemospermia was common, but typically self-limiting.

An additional, but rare, adverse event is needle-tract seeding. In a review of data to 2015, Volanis et al. (2015) reported a total of 40 incidences resultant from TRUSGB (n=9) and TPUSGB (n=31) (Volanis et al. 2015). It should be noted however, that current evidence on needle-tract seeding in prostate biopsy is poor and relies on case report evidence.

B7.5 OTHER ISSUES CONCERNING THE SAFETY PROSTATE BIOPSY

INFECTION AND ANTIBIOTIC PROPHYLAXIS

Antibiotic use for prostate biopsy is essential (Yaghi and Kehinde 2015), and reduces the chance of infection from trans-rectal biopsy to less than five per cent (Kapoor et al. 1998; Utrera et al. 2011a). Currently Ciprofloxacin appears to be the antibiotic most commonly used as *Escherichia coli* is the most common organism implicated in post biopsy infection (Zaytoun et al. 2011). Infection rates may be increasing (Carignan et al. 2012) and recent overseas travel or antibiotic use are independent risk factors for severe infection due to antibiotic resistance after prostate biopsy, with a 2.7 and 4 times greater risk, respectively (Patel et al. 2012).

In Australian clinical practice antibiotics are always used before biopsy (Applicant 2016). In trans-rectal biopsy usually oral antibiotics are given for several days pre and post procedure as well as a single intravenous dose during procedure, to reduce the risk of infection. In trans-perineal biopsy there is still a risk of infection but not as great. A single intravenous dose of antibiotics is given during the procedure, but pre- and post-procedure oral antibiotics are not required.

PRE-BIOPSY WORKUP INCLUDING ENEMA

The pre-biopsy workup for both trans-rectal and trans-perineal biopsies also includes an enema. Enema, in addition to antibiotics, has been proven effective in decreasing rates of UTI (Kam et al. 2014; Simsir et al. 2010). In Australia enema is always given before trans-rectal or trans-perineal biopsy to reduce the risk of infection (Applicant 2016).

NUMBER OF CORES

It has been hypothesised that increasing number of needle cores in TRUSGB may be associated with increased risk of infection (Simsir et al. 2010). However, major infection is not common and a study with over 700 patients found an equal rate of sepsis in patients who had six- as compared to 12-core biopsy (Mohammed et al. 2016); another study comparing 6, 10 and 15-core biopsies in 5,957 patients found no statistically significant increase in morbidity with increasing cores (Berger et al. 2004). There is, at present, no quality evidence that increasing number of cores is associated with increased rates of infection (Stock et al. 2008). Advice from the Applicant is that in Australian clinical practice between 12 and 36 cores are taken in TRUSGB and TPUSGB, whereas between 2 and 3 cores are taken in MRIGB. For MRIGB, there may be some association between number of cores and infection risk; however, this is not based on published data (Applicant 2016).

B7.6 SUMMARY OF COMPARATIVE HARMS

Infection is the most significant issue in prostate biopsy as serious infection can lead to death. Not so significant issues include bleeding (haematuria, haemospermia, and haematochezias), and urinary obstruction. Infection is reduced by antibiotic prophylaxis and pre biopsy workup including enema. Trans-perineal biopsy results in less infection than TRUSGB.

B8 INTERPRETATION OF THE CLINICAL EVIDENCE

Population 1 Men with a suspicion of prostate cancer

While there is a high level of uncertainty around estimates of diagnostic accuracy of mpMRI for detecting PCa, there is evidence that any inferiority compared to TRUSGB or TPUSGB may not adversely affect patients' outcomes. On the basis of the evidence profile (summarised in Table 37), it is suggested that, relative to TRUSGB and TPUSGB, mpMRI has non-inferior effectiveness. However the uncertainty associated with the diagnostic accuracy of mpMRI indicates the unreliability of the technique at this time. It is suggested mpMRI has superior safety to TRUSGB; however, the adverse events associated with biopsy are generally minor and occur in a small proportion of patients.

Ten studies, including 2,062 patients, reported that a per-patient analysis of the diagnostic accuracy of mpMRI in patients suspected of having PCa were included in the meta-analysis for Population 1. Pathology of samples obtained by biopsy was the reference standard in all studies. The bivariate model was used to generate estimates of sensitivity and specificity. For the detection of PCa of any severity, mpMRI has a sensitivity of 73.4 per cent (95% CI [57.0, 85.1]) and a specificity of 77.1 per cent (95% CI [63.5, 86.7]). For the detection of clinically significant cancer mpMRI has a sensitivity of 76.3 per cent (95% CI [58.6, 88.0]) and a specificity of 82.9 per cent (95% CI [71.5, 90.4]).

The point estimates for sensitivity and specificity are associated with wide confidence intervals reflecting uncertainty in the results. Heterogeneity was not able to be explained through subgroup analysis of clinical features. Overall, the quality of the evidence base to inform the diagnostic accuracy outcomes was rated as 'low' using the GRADE tool.

It should also be noted that the diagnostic accuracy of TRUSGB is uncertain, and the impact this has had on the results of mpMRI is not known. There is no evidence that mpMRI is superior to TRUSGB or TPUSGB for the detection of any cancer or the detection of clinically significant cancer.

As discussed in Subsection B5, only patients at low-concern will experience a change in management and outcomes associated with the introduction of mpMRI. These patients will avoid a biopsy under the proposed algorithm. In this population, the reported prevalence of PCa is assumed to be 30 to 40 per cent (Applicant feedback).

Low-concern patients who receive a false negative mpMRI will experience a delay to treatment; it is not clear that this delay is associated with any adverse outcomes for patients, particularly those with low risk disease (Subsection B5). Advice from the Applicant is that most patients with low-concern will be diagnosed with low risk disease. The evidence base to inform patient outcomes following delayed treatment is considered very low quality and is based on observational evidence.

Low-concern patients who receive a negative mpMRI will avoid a biopsy. mpMRI is considered safe for most patients as no study was identified that reported any adverse event associated with its use. TRUSGB is associated with a rate of major infection ranging from 0-2 per cent and a rate of minor infection ranging from zero to seven per cent. By avoiding a biopsy, patients will avoid this risk. On the other hand, TPUSGB is not associated with major infection and minor infection was rarely reported. As the proportion of biopsies being performed trans-perineally in Australia is increasing, the risk of infection associated with biopsy is decreasing. Other harms associated with biopsy are described in Table 37. The evidence base to inform the harms associated with biopsy is considered low to very low quality and is informed by observational studies. Based on these results, it is suggested mpMRI has superior safety to TRUSGB; however, the adverse events associated with biopsy are generally minor and occur in a small proportion of patients.

Population 2 Men with low-risk prostate cancer on active surveillance

In Population 2 mpMRI was found to have inferior diagnostic accuracy compared to TRUSGB and TPUSGB; however, there is limited evidence that this would adversely affect patient outcomes. Based on the evidence profile (summarised in Table 38), it is suggested that, relative to TRUSGB and TPUSGB, mpMRI imaging and associated interventions have superior safety and non-inferior effectiveness.

Six studies, including 820 patients, were identified that reported a per-patient analysis of the diagnostic accuracy of mpMRI to detect upgraded cancer in patients on AS programs. Pathology of samples obtained by biopsy was the reference standard in three studies, while three studies used pathology of prostatectomy specimens. For the detection of cancer upgrade, mpMRI has a sensitivity of 79.3 per cent (95% CI [74.6, 83.3]) and a specificity of 55.1 per cent (95% CI [50.4, 59.8]). The narrow 95 per cent confidence and prediction regions reflects the high level of certainty in the point estimate and the low level of heterogeneity present in the evidence base. The evidence base for the diagnostic accuracy outcomes was rated as high quality using the GRADE tool.

As discussed in Subsection B6.8, only patients with low-concern who have a negative mpMRI will have a change in management under the proposed algorithm. These patients will avoid a biopsy. Advice from the Applicant is that the prevalence of upgraded disease in these patients is 30 per cent.

Patients who have a false negative mpMRI will have their treatment delayed and remain on AS. One observational study was identified that assessed the impact of delayed treatment in this population and the quality of evidence was rated very low using the GRADE tool. On this basis, mpMRI is considered non-inferior to TRUSGB and TPUSGB.

The relative safety of mpMRI and biopsy are discussed above for Population 1. There is no evidence that the relative harms associated with mpMRI and biopsy will be any different in Population 2 than those described above for Population 1, therefore mpMRI is suggested to have superior safety.

Table 37 Summary of findings for the linked evidence comparison of mpMRI, relative to TRUSGB or TPUSGB, in patients at low-concern with suspected prostate cancer with assumed pre-test probability (prevalence) of 35%

Outcomes	Patients/ Studies	Quality of evidence ^a	No. per 100 patients with intervention [95% CI] ^b	No. per 100 patients with comparator [95% CI] ^c	Importance	Comments
True positives	2,062 patients (10 studies).	⊕⊕⊖⊖	26 [20,30]	28 [25, 31]	Critical	Will undergo biopsy as under current management.
False positives	2,062 patients (10 studies).	⊕⊕⊖⊖	15 [9, 24]	0 [0, 0]	Critical	Will undergo biopsy as under current management.
True negatives	2,062 patients (10 studies).	⊕⊕⊖⊖	50 [41, 56]	65 [65, 65]	Critical	Will avoid biopsy adverse events.
False negatives	2,062 patients (10 studies).	⊕⊕⊖⊖	9 [5,15]	7 [4, 11]	Critical	Will avoid the adverse events of biopsy but possible detriment due to delayed treatment.
Major infection	45,492 patients (8 studies).	⊕⊕⊖⊖	0	TRUSGB: Range 0-2 TPUSGB: 0	Critical	-
Minor infection	132,239 patients (9 studies).	⊕⊕⊖⊖	0	TRUSGB: Range 0-7 TPUSGB: Range 0-1	Critical	-
Re-hospitalisation	292,956 patients (9 studies)	⊕⊕⊖⊖	0	TRUSGB: Range 0-6 TPUSGB: Range 1-2	Critical	-
Bleeding	334,688 patients (13 studies).	⊕⊖⊖⊖	0	TRUSGB: Range 1-88 TPUSGB: Range 1-6	Important	-
Urinary obstruction	132,020 patients (12 studies).	⊕⊖⊖⊖	0	TRUSGB: Range 1-21 TPUSGB: Range 0-38	Important	-
Overall survival	41,146 (5 studies).	⊕⊖⊖⊖	NA	NA	Critical	Delay did not impact overall survival (results from 5 studies).

Outcomes	Patients/ Studies	Quality of evidence ^a	No. per 100 patients with intervention [95% CI] ^b	No. per 100 patients with comparator [95% CI] ^c	Importance	Comments
Cancer-free survival	8,916 (2 studies).	⊕⊕⊕⊕	NA	NA	Critical	Delay did not impact cancer free survival (results from 2 studies).
Rate of metastases formation	6,681 patients (4 studies).	⊕⊕⊕⊕	NA	NA	Critical	Delay did not impact rate of metastases formation (results from 4 studies).
Rate of biochemical recurrence	19,768 patients (14 studies).	⊕⊕⊕⊕	NA	NA	Critical	3 studies reported recurrence was associated with delayed treatment, 11 studies reported no impact.
Rate of extra capsular extension	16,039 patients (7 studies).	⊕⊕⊕⊕	NA	NA	Important	Delay did not impact rate of extra-capsular extension (results from 7 studies).
Rate of lymph node involvement	3,605 patients (3 studies).	⊕⊕⊕⊕	NA	NA	Important	Delay did not impact rates of lymph node involvement (results from 3 studies).
Rate of positive surgical margins	14,413 patients (6 studies).	⊕⊕⊕⊕	NA	NA	Important	One study reported a delay >9 months was associated with an increase in the rate of positive surgical margins in patients with intermediate risk disease. 8 studies reported no impact from delayed treatment.

^a: GRADE Working Group grades of evidence (Guyatt et al. 2013).

⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.

⊕⊕⊕⊕ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

⊕⊕⊕⊕ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

⊕⊕⊕⊕ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

^b: A prevalence of PCa in low-concern patients of 30-40% was provided by the Applicant. The midpoint of this range has been used to inform these estimates. Only low-concern patients have been included in this assessment as there is no change in management for patients at high-concern, regardless of mpMRI results.

^c: Calculated using the reported sensitivity of TRUSGB biopsy of 0.81 (95% CI [0.70, 0.88] and assuming TRUSGB had a specificity of 100%.

TRUSGB = trans-rectal ultrasound-guided biopsy, TPUSGB = trans-perineal ultrasound-guided biopsy, NA = not applicable, CI = confidence interval,

Table 38 Summary of findings for the linked evidence comparison of mpMRI, relative to TRUSGB or TPUSGB, in patients on active surveillance with assumed pre-test probability (prevalence) for upgraded disease of 30%

Outcomes	Patients/Studies	Quality of evidence ^a	No. per 100 patients with intervention [95% CI] ^b	No. per 100 patients with comparator [95% CI] ^c	Importance	Comments
True positives	820 patients (6 studies).	⊕⊕⊕⊕	24 [22,35]	28 [25, 31]	Critical	Will undergo biopsy as under current management.
False positives	820 patients (6 studies).	⊕⊕⊕⊕	31 [28, 37]	0 [0, 0]	Critical	Will undergo biopsy as under current management.
True negatives	820 patients (6 studies).	⊕⊕⊕⊕	39 [35, 42]	65 [65, 65]	Critical	Will avoid biopsy adverse events.
False negatives	820 patients (6 studies).	⊕⊕⊕⊕	6 [5,8]	7 [4, 11]	Critical	Will avoid the adverse events of biopsy but possible detriment due to delayed treatment.
Positive surgical margins	219 patients (1 study).	⊕⊖⊖⊖	NA	NA	NA	There is no evidence that delayed treatment increases the rate of positive surgical margins.

^a: GRADE Working Group grades of evidence (Guyatt et al. 2013).

⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.

⊕⊕⊕⊖ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

⊕⊕⊖⊖ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

⊕⊖⊖⊖ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

^b: A prevalence of PCa upgrade in low-concern patients of 30% was provided by the Applicant. Only low-concern patients have been included in this assessment as there is no change in management for patients at high-concern, regardless of mpMRI results.

^c: Calculated using the reported sensitivity of TRUSGB biopsy of 0.81 (95% CI [0.70, 0.88] and assuming TRUSGB had a specificity of 100%
 TRUSGB = trans-rectal ultrasound-guided biopsy, TPUSGB = trans-perineal ultrasound-guided biopsy, NA = not applicable, CI = confidence interval.

C.1. OVERVIEW

The clinical evaluation presented in Section B concludes that compared to other clinical strategies, mpMRI is non-inferior with respect to accuracy and superior with respect to safety. Section D provides a model-based analysis to estimate the cost-effectiveness of mpMRI in the expected MBS population. Results are presented as incremental costs per quality of life-year (QALY) gained by using mpMRI compared to other clinical management strategies (TRUSGB or TPUSGB in Population 1, re-biopsy in Population 2). A decision tree was used to model the diagnostic pathways, followed by a Markov model representing subsequent follow-up (see Subsection D.3). Results from the studies presented in Section B were used to inform this model.

Subsection C.2 (applicability translation issues) addresses the following question: To what extent are the study results presented in the key trials from section B applicable to the Australian MBS setting?

The clinical outcomes presented in Section B provide information about test accuracy and safety, but not on the long-term impact on disease progression and mortality. To estimate the long-term impact of the use of mpMRI, accuracy results need to be translated into longer term outcomes, such as overall survival. Therefore, Subsection C.3 (extrapolation translation issues) addresses the following question: What is the impact of mpMRI on the prognosis of prostate cancer patients?

The economic evaluation will use QALYs gained as a summary measure of the impact of mpMRI on both the quality and quantity of patient lives, as none of the clinical accuracy studies measured impact on (short and long term) quality of life, Subsection C.4 (transformation issues) provides utility values that are used to transform the impact of mpMRI on safety and survival into QALYs.

In order to give a balanced overview of all costs and effects associated with mpMRI, the economic evaluation includes the costs and effects of adverse events related to mpMRI and biopsies. Subsection C.5 will therefore address the question: How can the economic model in Section D incorporate the safety of mpMRI and biopsy procedures?

Subsection C.6 summarises how the various issues discussed in Section C are incorporated into the economic evaluation in Section D.

A summary of translation issues addressed in this section is presented in Table 39.

Table 39 Summary of translation issues

Applicability issues	Methods, data and sources	Section
Population and intervention characteristics To what extent are the study results presented in the key trials in section B applicable to the Australian MBS setting?	Descriptive comparison between the patients enrolled in the pivotal trials and intervention characteristics (Section B) and the expected MBS population and setting using Australian registry data.	Subsection C.2
Extrapolation issues		
Prognosis What is the impact of mpMRI on the prognosis of prostate cancer patients?	Analysis based on Section B and additional literature review.	Subsection C.3
Transformation issues		
Utility What are the disutilities associated with the various health states?	Analysis based on targeted literature review.	Subsection C.4
Other translation issues		
Safety How can the economic model in Section D incorporate the safety of mpMRI and biopsy procedures as presented in section B?	Analysis based on safety data from Section B.	Subsection C.5

MBS = Medical Benefits Schedule, mpMRI = multiparametric MRI.

C.2. APPLICABILITY TRANSLATION ISSUES

In order to evaluate the applicability of the clinical evidence to the expected MBS populations, patient characteristics and intervention characteristics from the key studies were compared to the patient and intervention characteristics in the expected MBS population. This was done for Population 1 and Population 2 separately.

POPULATION 1: (MEN WITH SUSPECTED PROSTATE CANCER): PATIENT CHARACTERISTICS

The following population characteristics were assessed in Population 1: country, age, prior tests, PSA level and clinical algorithm (see Table 40).

Table 40 Population characteristics, comparison between key clinical studies and the expected MBS Population 1

Study ID (n)	Country	Age (years)	Prior tests	PSA level (ng/ml)
Australian registry data				
Victorian Prostate Cancer Clinical Registry (Evans et al. 2013; Victorian Prostate Cancer Clinical Registry Steering Committee 2015) Cumulative number of participants in 2013, n=2,198	Australia	Mean 66 (age at diagnosis)	NR	Median 7.8
The South Australian Prostate Cancer Clinical Outcomes Collaborative (Kinnear et al. 2016; Ruseckaite et al. 2016; SA Prostate Cancer Clinical Outcomes Collaborative 2014) n=915	Australia	Mean 67(age at diagnosis)	NR	Median 6.5
Farrugia et al. Cancer Institute NSW (Sydney South West) (Farrugia et al. Unk) n=513	Australia	Mean 69 (age at diagnosis)	NR	NR
Section B key trials				
Baldisserotto et al. (2016) n=54	Brazil	Mean 66	PSA, DRE	Mean 8.4
Baur et al. (2016) n=45	Germany	Mean 66	PSA, DRE, biopsy	Mean 12.3
Dikaios et al. (2015) n=85	UK	Mean 63	PSA, DRE	Mean 8.66
Jambor et al. (2015) n=55	Finland	Median 66	PSA, DRE	Median 7.4
Lista et al. (2015) n=150	Spain	Mean 66	PSA, DRE, biopsy	Mean 11.3
Pokorny et al. (2014) n=226, 3 withdrew	Australia	Median 63	PSA, DRE	Median 5.3
Thompson et al. (2014) n=150	Australia	Median 62	PSA, DRE	Median 5.6
Thompson et al. (2016) n=344	Australia	Median 63	PSA, DRE	Median 5.2
Wang et al. (2015) n=1,113 (but only 586 biopsied within 3 months of MRI)	China	Mean 70	DRE, PSA	NR
Zhao et al. (2016) n=372	China	Mean 69	DRE, PSA	Mean 15.0

DRE = digital rectal examination, NR = not reported, PSA = prostate-specific antigen.

Section B included 10 key studies that included Population 1, of these three were conducted in Australia. Therefore, a substantial part of the clinical data was collected in Australia. In general, for the three Australian studies (Pokorny et al. 2014; Thompson et al. 2014; Thompson et al. 2016) the pooled estimate of sensitivity (54.3%, 95% CI [38.3, 69.5]) was lower than pooled estimate of sensitivity demonstrated overall in the key clinical studies (73.4%, 95% CI [57.0%, 85.1]). The specificity in the Australian studies (87.2%, 95% CI [4.8, 94]) was higher than specificity in the key

clinical studies (77.1%, 95% CI [63.5, 86.7]). To test the impact of this on the ICER, a sensitivity analysis was performed using accuracy results from the sub selection of Australian studies (sensitivity analysis B, see Subsection D.6).

Although the age of the expected Australian Population 1 is unknown, the mean age at diagnosis of prostate cancer was between 66-69 years in the Australian registries. The mean age of the key study populations ranged between 62 and 70. Therefore, the age of the expected MBS population lies within this range.

The key studies differed in the tests participants received prior to mpMRI. In all studies patients had received PSA and DRE. This is consistent with the clinical management algorithm for the MBS population, which requires PSA/DRE in order to undergo mpMRI. In two studies, patients received biopsy (negative result) in addition to PSA/DRE. A proportion of the expected MBS population may also have had a previous biopsy with negative result and subsequent follow-up with PSA testing.

In the key clinical studies that reported median PSA levels these ranged from 5.2ng/ml to 7.4ng/ml. In the Australian registries, median PSA levels (at diagnosis) were 6.5ng/ml (South Australia) and 6.8 ng/ml (Victoria) which is within the range of key trial values.

According to the proposed clinical algorithm, the expected MBS population will be pre-selected before undergoing mpMRI (PSA >3 ng/ml or lower level if <50 years of age, or positive family history, or free/total ratio $<25\%$). In many of the key clinical studies it was unclear whether the study populations would meet these criteria. Therefore, baseline prostate cancer risk in the study populations may differ from the baseline risk in the expected MBS population. This is not expected to impact the economic evaluation, since test sensitivity and specificity are independent of disease prevalence. The economic model in Section D used Australian prevalence data. However, different pre-selection may result in different tumour characteristics (e.g. tumour size), which may impact test accuracy.

In conclusion, comparison of population characteristics between the key clinical studies and Australian registry data did not identify any consequential applicability issues. However, differences in patient pre-selection for mpMRI may impact test accuracy. Since the extent of this impact is unknown, sensitivity analyses were performed to evaluate the impact of reduced and increased test accuracy on the cost-effectiveness of mpMRI. Sensitivity analyses were also performed for accuracy based on the sub-selection of Australian studies only.

POPULATION 1: INTERVENTION CHARACTERISTICS

The following intervention characteristics were assessed in Population 1: type of MRI machine, use of an endorectal coil, type of imaging (T1, T2, DCE, DWI), type of contrast, PI-RADS cut-off value and reader experience (see Table 41).

Table 41 Intervention (mpMRI) characteristics, comparison between key clinical studies and the expected MBS Population 1

Study ID (n)	MRI type	Endorectal coil used Y/N	Type of imaging	Contrast	Reader experience
Baldisserotto et al. (2016) n=54	3	N	T2W, DWI, DCE	NR	2 urologists, 1 with 10 years' experience, 1 with 1 year post-residency experience
Baur et al. (2016) n=45	3	N	T2W, DWI, DCE	Gadobutrol	2 readers with 3 and 5 years' experience in prostate imaging
Dikaivos et al. (2015) n=85	1.5	N	T2W, DWI, DCE	Gadolinium contrast	2 radiologists with 5 and 7 years mp MRI experience
Jambor et al. (2015) n=55	3	N	T2W, DWI, DCE	Dotarem or Gadovist	NR
Lista et al. (2015) n=150	1.5	Y	T2W, DWI, DCE	NR	NR
Pokorny et al. (2014) n=226, 3 withdrew	3	N	NR	NR	3 radiologists with: 1 year, 1 year and 19 years' experience respectively in consensus
Thompson et al. (2014) n=150	1.5 or 3.0	N	T2W, DWI, DCE	Gadolinium diethylenetriaminepentaacetate acid	2 radiologists with >1000 prior prostate mpMRIs
Thompson et al. (2016) n=344	1.5 or 3.0	N	T2W, DWI, DCE	Gadolinium diethylenetriaminepentaacetate acid	2 radiologists with >1000 prior prostate mpMRIs
Wang et al. (2015) n=1,113 (but only 586 biopsied within 3 months of MRI)	1.5	Y	T2W, DWI, DCE	Gadopentetic dimeglumine	2 radiologists with 10 and 3 years' experience
Zhao et al. (2016) n=372	3	N	T2W, DWI, DCE	NR	2 radiologists experienced in PI-RADS v2

DCE = dynamic-contrast enhanced, DWI = diffusion weighted imaging, T2W = T2 weighted, PI-RADS = Prostate imaging reported and data system, mpMRI = multiparametric MRI, MRI = magnetic resonance imaging, NR =not reported.

The key clinical studies used a variety of MRI scanners, both 1.5 and 3.0 Tesla, both of which are currently available in Australia (HealthPACT 2015). Only 2 out of the 10 key studies used an endorectal coil for mpMRI. This is consistent with the expected MBS population, where an endorectal coil will likely be used in only few cases (Applicant 2016).

The Protocol defines mpMRI to use three pulse sequences T2W, DWI, DCE. Each of the key clinical studies used these same techniques; noting Pokorny et al. (2014) did not explicitly report the type of mpMRI imaging. The type of contrast agent used was not consistently reported, but, when defined, a gadolinium contrast agent was used; this is consistent with the expected MBS population.

The PI-RADS cut-off value differed between studies. As the proposed clinical management algorithm prescribes PI-RADS ≥ 4 as cut-off, only key studies using this cut-off value were included (see Subsection B.3).

Reader experience differed between the key clinical studies, but was generally reported to be substantial. Study results may therefore reflect that mpMRI accuracy is conditional on sufficient reader experience. If items for prostate mpMRI are listed on the MBS, the average Australian reader experience may be lower than in the key clinical studies, given that the studies were likely performed by early adopters. It should be noted that the general Australian reader experience is likely to be lower, and therefore their initial accuracy may also be lower. Similarly, if case accuracy increases over time, cost-effectiveness will also increase over time. The results from the base-case economic evaluation may therefore reflect longer-term cost-effectiveness instead of initial cost-effectiveness.

In conclusion, comparison of intervention characteristics between the key clinical studies and the expected MBS population did not identify any overt applicability issues. To ensure applicability to the intended MBS population, only studies using PI-RADS ≥ 4 as a cut-off were included. The mpMRI cost-effectiveness results may be conditional on sufficient reader experience since the accuracy studies generally used experienced readers. This issue was addressed by performing sensitivity analyses to evaluate the impact of reduced and increased test accuracy on the cost-effectiveness of mpMRI (see Subsection D.6).

POPULATION 2: (MEN WITH LOW OR INTERMEDIATE RISK PROSTATE CANCER UNDER ACTIVE SURVEILLANCE):

PATIENT CHARACTERISTICS

In Population 2, the following patient characteristics were assessed: country, age, prior tests, PSA level and Gleason score (see Table 42).

Table 42 Population characteristics, comparison between key clinical studies and the expected MBS Population 2

Study ID (n)	Country	Age	Prior tests	PSA level	Gleason score
Australian registry data					
Victorian Prostate Cancer Clinical Registry, (Weerakoon et al. 2015) n=980	Australia	Median 66	NR	Reported per risk category.	Reported per risk category.
Section B key trials					
Abd-Alazeez et al. (2014) n=137	UK	Mean between 59 and 63, dependent on mpMRI outcome.	Prior biopsy, PSA	Median between 5 and 8, dependent on mpMRI outcome.	All 3+3
Almeida et al. (2016) n=73	Italy	Mean 63	Prior biopsy, PSA	Mean 6.0	≤ 6

Study ID (n)	Country	Age	Prior tests	PSA level	Gleason score
de Cobelli et al. (2015) n=223	Italy	Mean 63	Prior biopsy, PSA	Mean 6.0	≤6
Flavell et al. (2014) n=64	USA	Median 61	PSA, biopsy	Median 4.7	All 3+3
Porpiglia et al. (2015) n=120	Italy	Median 65 or 66, dependent on cancer significance.	PSA, PHI, PCA3, biopsy	Median 5.8 or 7.0, dependent on cancer significance.	All ≤6
Recabal et al. (2016) n=206	USA	Median 63	PSA, PHI, biopsy	Median 5.2	All ≤6

PCA3 = prostate cancer gene 3; PHI = prostate health index; PSA = prostate-specific antigen, mpMRI = multiparametric MRI.

Section B included 6 key studies that included Population 2. The studies were conducted in UK, Italy and the USA. Information about the Australian AS population was obtained from a publication by the Victorian Prostate Cancer Registry (Weerakoon et al. 2015). The median age within the Australian registry was 66 years. The key clinical studies that reported median age included values between 61 and 66 years. Weerakoon et al. (2015) reported that there are patients included in the Australian registry who received AS despite having significant (intermediate to high risk) cancer. This population is not included in the proposed MBS item for AS with mpMRI. The economic evaluation assumed the use of mpMRI in Population 2 for low to intermediate risk patients only, consistent with the proposed indication and the clinical trials.

In all key clinical studies for Population 2, patients previously received PSA testing and biopsy, consistent with the expected MBS population. In two studies, additional tests were performed (e.g. prostate health index), but patients were not selected for mpMRI based on these results.

Median PSA score ranged between 4.7 and 8ng/ml in the key clinical studies. Mean or median PSA score was not reported for the AS population in the Australian registry. A PSA <10ng/ml was reported for 100 per cent of the low risk cancer patients and 54 per cent of the intermediate risk cancer patients under AS. Gleason score was ≤6 in all key clinical studies and for all of the low risk patients enrolled in the Australian registry. However, it was higher for 64 per cent of the intermediate risk patients receiving AS in the Australian registry. While the AS population in the key clinical studies is from low risk men, the AS population in Australian clinical practice includes intermediate risk men (and some high risk men) as well. This may reduce the applicability of the accuracy results. It is important to note that men with intermediate to high risk prostate cancer are not eligible for mpMRI under the requested MBS listing.

In conclusion, population characteristics in the key clinical studies are similar to the expected MBS population with low to intermediate risk cancer. However, the Australian AS population includes a higher proportion of men with intermediate and high risk cancer. Given their different characteristics, the mpMRI accuracy results may not be applicable to the population at higher risk of cancer progression; however, high risk men are ineligible for AS with mpMRI.

POPULATION 2: INTERVENTION CHARACTERISTICS

In Population 2, the following intervention characteristics were assessed: type of MRI machine, use of an endorectal coil, type of imaging (T1, T2, DCE, DWI), type of contrast, PI-RADS cut-off value and reader experience (see Table 43).

Table 43 Intervention (mpMRI) characteristics, comparison between key clinical studies and the expected MBS Population 2

Study ID [N]	MRI type	Endorectal coil used Y/N?	Type of imaging	Contrast	Reader experience
Abd-Alazeez et al. (2014) n=137	1.5 or 3.0	N	T2W, DWI, DCE	meglumine gadoterate	5 radiologists who have experience reporting at least 100 mpMRIs per year
Almeida et al. (2016) n=73	1.5	N	T2W, DWI, DCE	gadopentetate dimeglumine	2 radiologists experienced in prostate MRI in consensus
de Cobelli et al. (2015) n=223	1.5	Y	T2W, DWI, DCE	gadopentetate dimeglumine	NR
Flavell et al. (2014) n=64	1.5 or 3.0	Y	T1W, T2W, DWI - not DCE	NA	2 radiologists with 2 and 15 years experience in consensus
Porpiglia et al. (2015) n=120	1.5	Y	T1W, T2W, DWI, DCE	NR	2 experienced radiologists
Recabal et al. (2016) n=206	1.5 or 3.0	Y and N	T1W, T2W, DWI, DCE	NR	6 radiologists with 6 to 15 years experience

DCE = dynamic-contrast enhanced, DWI = diffusion weighted imaging, MRI = magnetic resonance imaging, T2W = T2 weighted, T1W = T1 weighted, NR = not reported.

As with Population 1, the key clinical studies in Population 2 used 1.5 and/or 3.0T scanner, both are currently available in Australia (HealthPACT 2015). In the studies for Population 2, the use of an endorectal coil was more common than in the studies for Population 1.

Three of six studies used imaging techniques (T2W, DCE, DWI) consistent with the expected MBS population. The other studies also used T1W imaging; and, one study Flavell et al. (2014) did not include DCE, which may reduce test accuracy. The type of contrast agent used was not consistently reported, but, when defined, a gadolinium contrast agent was used; this is consistent with the expected MBS population.

PI-RADS cut-off value differed between studies. However, the proposed clinical management algorithm prescribes PI-RADS ≥ 4 as cut-off. Therefore, consistent with the approach in Population 1, only key studies using this same cut-off value were included (see Subsection B.3).

Similar to the studies in Population 1, reader experience differed between key studies and was generally reported to be substantial. The results from the economic evaluation may therefore reflect longer-term cost-effectiveness instead of initial cost-effectiveness.

In conclusion, comparison of intervention characteristics between the key clinical studies and the expected MBS population did not identify overt applicability issues. To ensure applicability, only studies using PI-RADS ≥ 4 as cut-off were included. The mpMRI cost-effectiveness results may be conditional on sufficient reader experience since the accuracy studies generally used experienced readers. This issue was addressed by performing sensitivity analyses to evaluate the impact of reduced and increased test accuracy on the cost-effectiveness of mpMRI (see Subsection D.6).

C.3. EXTRAPOLATION TRANSLATION ISSUES

This section considers the impact of mpMRI on the prognosis of PCa patients.

None of the key accuracy studies discussed in Section B measured the impact of mpMRI on PCa progression and/or mortality. Prognostic information was therefore sourced from other literature, aligning with the sources used in the evaluation of MRIGB procedures for diagnosis of PCa (CA 1424). Probability of developing cancer whilst receiving PSA screening (9.7%) was obtained from (Gann et al. 2010). Probabilities of PCa progression were 8.8% for upstaging while under AS (Simpkin et al. 2015) and 2.6% for further progression to advanced prostate cancer (Bill-Axelson et al. 2014). Probabilities of PCa death were obtained from SEER data from the US (0.6% for patients with localised disease) and a meta-analysis from the prostate cancer trialists collaborative group (22% for patients with advanced disease). Australian Bureau of Statistics life tables were used to calculate age-related background mortality.

Given that the sensitivity and specificity of mpMRI and biopsies is lower than 100 per cent, a proportion of patients will be falsely classified as either negative or positive for prostate cancer. Additional costs were allocated to these patients to allow for the additional diagnostic tests needed to correct the false diagnosis (see Subsection D.4). Both for false negatives and false positives, the error was assumed to be corrected without a negative impact on prognosis. This assumption was made since there is insufficient evidence to support an impact of treatment delay on disease progression and mortality (see below and in Subsection B.5). A sensitivity analysis (see Subsection D.6) evaluates the potential impact of assuming an increased risk of disease progression for the subgroup of high risk PCa patients who experience treatment delay due to false negative prognosis.

In Population 1, one systematic review (including 17 studies) and eight additional primary studies were identified that assessed the impact of delayed treatment on patient outcomes. For men with low risk disease (Gleason ≤ 6) there is evidence that a delay to surgery may be associated with an upgrading of Gleason score; however, there is considerable evidence that delayed treatment is not associated with an increase in rates of biochemical recurrence, positive surgical margins or extra-

capsular extension. This is consistent with current management of patients with low risk disease; i.e. enrolment in an AS program. For men with intermediate or high risk disease in Population 1, there may be adverse outcomes associated with delayed treatment; however, the evidence in this group is mixed. One recent study by Dong et al. (2016) assessed outcomes for 4,064 men with low (n=1,549), intermediate (n=1,612) and high risk (n=903) PCa. The length of delay measured in this study was up to 24 months. Dong et al. (2016) found no impact resultant from delays (up to 24 months) in patients with any prostate cancer risk classification.

In Population 2, evidence is limited. One study was identified that found no difference in outcomes associated with a delay (see Subsection B.5).

C.4. TRANSFORMATION ISSUES

QUALITY OF LIFE

Quality of life data were not collected in the studies presented in Section B. Therefore to obtain suitable utility/disutility values for the various health states presented in the economic model (Subsection D.4), targeted literature searches were conducted in the following databases:

- Cost-Effectiveness Analysis Registry (CEA Registry); and,
- PubMed.

Additionally, utility values were sourced from the selected economic evaluations identified in the systematic literature search (Subsection D.3). Utility values were aligned with the values used in the parallel application for MRI guided biopsy CA 1424. Studies reporting Australia-specific utility values or including Australian populations were retained in the search.

Studies were retained for inclusion if they reported utility values for populations consisting of:

- Patients with low/intermediate risk prostate cancer on active AS;
- Patients with high/intermediate risk prostate cancer receiving active treatment/follow-up;
- Men receiving prostate biopsy;
- Patients with AEs due to prostate biopsy and/or PCa related treatment: sepsis; erectile dysfunction and urinary incontinence.
- A general Australian population of males aged ~66 years.

A summary of the key studies identified in the targeted literature search for utility values are provided in Table 44.

Table 44 Results of utility literature search

Inclusion criteria	Citations
Low/intermediate risk PCa on AS;	Stewart et al. (2005)
High/intermediate risk PCa receiving active treatment/follow-up;	Stewart et al. (2005)
Advanced PCa;	Stewart et al. (2005), Sullivan et al. (2007)
Prostate biopsy;	Zhang 2012
AEs: sepsis, erectile dysfunction, and urinary incontinence;	Cooperberg et al. (2013), Stevenson et al. (2014)
General Australian population of males aged above ~66 years.	Clemens et al. (2014), Norman et al. (2013)
Included	7

AE = adverse event, PCa = prostate cancer.

Utility values for each health state listed in Table 45 were extracted from the seven studies noted above. Two studies identified measured utility values in a general population (Clemens et al. 2014; Norman et al. 2013). Norman et al. (2013) reported utility values for a general Australian population of males aged between 60 to 70 years using the SF-36 instrument. Clemens et al. (2014) reported utility values for a general Australian male population aged 65 to 74 years. The values reported by Clemens et al. (2014) were used in the economic evaluation selection of general population as this is consistent with the evaluation of MR-guided biopsy procedures for diagnosis of PCa (CA 1424) and is a conservative approach. Given that Clemens et al. (2014) reported a utility value for the general population of interest, this has been used as the basis for the “alive without prostate cancer” health state in the economic model.

For PCa health states, the economic evaluation by de Rooij et al. (2014) (see Subsection D.3) applied utilities obtained from the study by Stewart et al. (2005) (de Rooij et al. 2014). Stewart et al. (2005) was also selected for the economic evaluation in this report as the reported utility values matched the health states in our economic model. The study used a standard gamble methodology to elicit utility values for different health states in PCa for men aged 60 and older (n=162). For the advanced PCa health state, a utility decrement was also obtained (Stewart et al. 2005). This utility was similar (0.67 versus 0.66) to the utility derived by Sullivan et al. (2007), who reported values for an Australian subgroup of male patients with metastatic hormone refractory prostate cancer (Sullivan et al. 2007). Furthermore, decrements at 3, 6 and 9 months after treatment are reported in this study for the entire study population (n=280) which included Australian patients (n=40).

The following methods were used to calculate health state values:

- Low/intermediate risk PCa on AS: Stewart et al. (2005) reported mean utility values for three health states consisting of men living with symptom-free cancer under conservative

management. As only one health state for patients with low/intermediate risk PCa is included in the economic model, a weighted average [using SUMPRODUCT in excel] of the mean utility values of the three health states was derived.

- High/intermediate risk PCa receiving active treatment/follow-up: Stewart et al. (2005) reported separate utility values for patient groups receiving either: hormone medications; orchiectomy; radiation therapy; prostatectomy; or transurethral resection prostatectomy (TURP). There is only one health state for high/intermediate risk PCa in the economic model presented in Section D. As this includes all treatments in the clinical algorithm (Figures 1 and 2, Section A), a weighted average [using SUMPRODUCT in excel] of the mean utility values of the five health states was derived.
- Advanced PCa: Stewart et al. (2005) and Sullivan et al. (2007) reported similar values for patients with advanced PCa (0.67 and 0.66 respectively). The utility reported by Stewart (2005) is consistent with the value used in CA 1424.

Consistent with the evaluation of MR-guided biopsy procedures for diagnosis of PCa (CA 1424), a one-off disutility associated with prostate biopsy was included in the economic evaluation, independent of biopsy type. No empirical data was available to estimate the size of this disutility. Previous authors (Zhang et al. 2012) have assumed a disutility of 0.05 for prostate cancer biopsy, based on values found in breast cancer. In our economic evaluation the disutility was assumed to be 0.035 to be consistent with the evaluation of MR-guided biopsy procedures for diagnosis of PCa (CA 1424). This disutility for biopsy is varied between 0 and 0.05 in sensitivity analyses (see Subsection D.6).

Table 45 Utility values used in the economic model

Health state	Utility value, mean (SD) [95%CI]	n	Source
General Australian population of males aged 61–70y	0.82 (NR) (0.80–0.84)	599	Clemens et al. (2014)
Low/intermediate risk PCa on AS			
1) PCa, 20% chance of spread, AS	0.84 (0.19)	88	Stewart et al. (2005)
2) PCa, 40% chance of spread, AS	0.81 (0.18)	49	Stewart et al. (2005)
3) PCa, 75% chance of spread, AS	0.71 (0.24)	53	Stewart et al. (2005)
4) States including chance of spread (25-75%)	0.796		weighted average
High/intermediate risk PCa receiving active treatment/follow-up;			
1) treatment, hormone medications	0.83 (0.19)	44	Stewart et al. (2005)
2) treatment, orchiectomy	0.87 (0.16)	38	Stewart et al. (2005)

Health state	Utility value, mean (SD) [95%CI]	n	Source
3) treatment, radiation therapy	0.73 (0.3)	44	Stewart et al. (2005)
4) treatment, prostatectomy	0.67 (0.29)	51	Stewart et al. (2005)
5) treatment, TURP	0.86 (0.16)	53	Stewart et al. (2005)
6) <i>weighted average of treatment states</i>	0.789		<i>weighted average</i>
Advanced PCa	0.67 (0.24)	46	Stewart et al. (2005)
Advanced PCa (MCRPCa)	0.66 (NR)	40	Sullivan et al. (2007)
Disutility of biopsy (one-off)	0.035	NA	Assumption informed by Zhang et al. (2012)
Disutility due to AEs			Assumptions informed by:
Acute sepsis ^a	-0.43 (assumed duration 1 month)	NA	Stevenson et al. (2014)
Erectile dysfunction [due to PCa treatment]	-0.10 [0.05; 0.15] (assumed duration 1 year)	NA	Cooperberg et al. (2013)
Urinary incontinence [due to PCa treatment]	-0.20 [0.1; 0.3] (assumed duration 1 year)	NA	Cooperberg et al. (2013)

^a: Stevenson et al. (2014) reported the utility associated with sepsis to be 0.47, with a utility of 1 for the healthy population. Therefore, the disutility of having acute sepsis is 0.53. This was multiplied by 0.82 (general population utility) to adjust for scale.

AE = adverse event, AS = active surveillance, MCRPCa = metastatic castrate-resistant prostate cancer, NA = not applicable, NR = not reported, PCa = prostate cancer, TURP = transurethral resection of the prostate.

C.5. ANY OTHER TRANSLATION ISSUES

Subsection B.7 discusses the adverse events associated with mpMRI and the various biopsy procedures. The mpMRI was not associated with any adverse events that were expected to substantially impact costs or benefits within the economic evaluation. Adverse reactions to the contrast agent have been documented but are rare when appropriate measures are taken (i.e. no gadolinium contrast for patients with renal failure) (see Subsection B.7). Therefore, the economic evaluation did not include costs or disutilities for mpMRI associated adverse events.

Biopsy-related adverse events are more common. Sepsis was considered to be a serious event with an associated cost and disutility. In the economic evaluation, the incidence of sepsis was assumed to be 1.2 per cent for all biopsy measures (Leahy et al. 2015). Although this estimate is for TRUSGB, it was assumed this probability of sepsis applies for all biopsy measures, consistent with the assumption made in the evaluation of MRIGB procedures for diagnosis of prostate cancer (CA 1424).

In addition to biopsy-associated sepsis, the economic evaluation took into account common adverse events associated with prostate cancer treatments. Consistent with the evaluation of MRIGB procedures for diagnosis of prostate cancer, these adverse events were assumed to be erectile

dysfunction and urinary incontinence with disutilities of 0.1 and 0.2 per cent respectively (Cooperberg et al. 2013). For the probabilities of these treatment-related complications, an Australian quality of life study from the New South Wales Cancer Registry paper (Smith et al. 2009) was used. The probability of erectile dysfunction was 50 per cent for radical prostatectomy and 33 per cent for external beam radiotherapy, with a weighted (50/50, see Subsection D.4) average of 41.5 per cent in the “intermediate to high risk prostate cancer” health state. The probability of urinary incontinence was 10 per cent for radical prostatectomy and 2.4 per cent for external beam radiotherapy, with a weighted (50/50, see Subsection D.4) average of 6.2 per cent in the “intermediate to high risk prostate cancer” health state.

C.6. RELATIONSHIP OF EACH PRE-MODELLING STUDY TO THE ECONOMIC EVALUATION

A summary of each of the translational issues discussed in Section C and their use in Section D is provided in Table 46.

Table 46 Example of summary of results of pre-modelling studies and their uses in the economic evaluation

Section	Pre-modelling study	Results used in Section D	Cross-reference	Results used in Subsection D.6	Cross-reference
Applicability					
Subsection C.2	Comparison of patient and intervention characteristics between the key clinical studies and Australian registry data, Population 1	The economic model is based on the Australian patient population.	D.2	Sensitivity analyses will be performed with the lower and upper values of the 95% CIs for accuracy results. Also, Australia-specific accuracy results will be used (sensitivity 54.3%, specificity 87.2%), obtained from a subsample of three, Australian studies.	D.6
Subsection C.2	Comparison of patient and intervention characteristics between the key clinical studies and Australian registry data, Population 2	The economic model is based on the Australian patient population.	D.2	Sensitivity analyses will be performed with the lower and upper values of the 95% CIs for accuracy results.	D.6
Extrapolation					

Section	Pre-modelling study	Results used in Section D	Cross-reference	Results used in Subsection D.6	Cross-reference
Subsection C.3	Literature review for prostate cancer mortality and the impact of false diagnosis on prognosis.	Alignment of transition probabilities with the evaluation for MR-guided biopsy procedures for diagnosis of PCa (CA 1424). No impact of false diagnosis on prognosis.	D.4	None	NA
Transformation					
Subsection C.4	Targeted literature review for utility values	General Australian population of males aged 61-70y, 0.82; low/intermediate risk PCa on AS, 0.796; high/intermediate risk PCa receiving Active treatment/ follow-up, 0.789; disutility of biopsy, 0.035; acute sepsis, 0.47; erectile dysfunction, 0.10; urinary incontinence, 0.20	D.4	The disutility associated with prostate biopsy will be varied in sensitivity analyses, between 0 and 0.05, consistent with the assessment of MRIGB (CA 1424).	D.6
Other					
Subsection C.5	Literature review for the frequencies of adverse events.	mpMRI: no adverse events. Biopsy: 1.2% sepsis. Prostate cancer treatment: 25.9% erectile dysfunction (1-year disutility) and 0.55% urinary incontinence (1-year disutility).	D.4	None	NA

AS = active surveillance, CI = confidence interval, mpMRI = multiparametric MRI, PCa = prostate cancer, MRIGB = MRI guided biopsy, CA = contracted assessment.

SECTION D

ECONOMIC EVALUATION

D.1. OVERVIEW

A clinical claim in the Protocol (p15) is that mpMRI scans of the prostate are more accurate and safer than usual care (TRUSGB or TPUSGB, Subsection A.5). The clinical evaluation in Section B suggests that, relative to current clinical management using TRUSGB or TPUSGB, pre-selection with mpMRI has superior safety and non-inferior effectiveness.

A summary of the evidence about the diagnostic accuracy, benefit and safety of mpMRI compared to TRUSGB or TPUSGB in Population 1 (men with suspected prostate cancer) and Population 2 (men with low or intermediate risk prostate cancer under AS) is presented in Table 47 below.

Table 47 Summary of evidence for mpMRI versus TRUSGB or TPUSGB

Population	Diagnostic accuracy		Observed benefit from clinical trials	Safety outcomes
	sensitivity	specificity		
Population 1: men with suspected prostate cancer	mpMRI non-inferior	mpMRI non-inferior	Prostate biopsies avoided	mpMRI superior
Population 2: men under AS	mpMRI non-inferior	mpMRI non-inferior	Prostate biopsies avoided	mpMRI superior

mpMRI = multiparametric MRI, TPUSGB = trans-perineal ultrasound guided biopsy, TRUSGB = trans-rectal ultrasound guided biopsy, AS = active surveillance.

To quantify the trade-off between mpMRI costs and benefits, a cost-utility analysis was undertaken. The benefits of mpMRI in the model are associated with avoiding biopsies and overtreatment associated with low to intermediate risk PCa in a proportion of the population.

The aim of the modelled economic evaluation is to estimate the cost-utility of mpMRI in two populations consisting of men with suspected PCa and men with PCa undergoing AS. One model was developed to examine the cost-utility of mpMRI in both populations. Data to inform the assumptions of the model were from the studies discussed in Sections B and C. Where data was unavailable, expert opinion has been sought.

This technology assessment is specific to mpMRI being used in the diagnostic pathway of PCa. As biopsy with TRUSGB, TPUSGB and MRIGB are part of the clinical management algorithm, they are included in the assessment. However, the assumptions and structure of the economic evaluation in this assessment aim to evaluate to use of mpMRI and not MRIGB, which is being assessed in a separate evaluation (CA 1424).

D.2. POPULATIONS AND SETTINGS

One economic model is presented which includes both Population 1 and Population 2. The cohort of patients entering the model consists of Australian men aged 66 years, which is the mean age of PCa diagnosis in Australia as obtained from the Victorian Prostate Cancer registry (Victorian Prostate Cancer Clinical Registry Steering Committee 2015). Patients in the cohort age over time in the model, and background mortality changes accordingly. Details of the applicability of the modelled population to the expected MBS population (demographic and patient characteristics) are presented in Section C. The structure of the economic model is presented in Subsection D.3.

In the specific modelled population, patients presenting with a high or concerning PSA/DRE are selected for further investigations in the model. Results for the economic evaluation are presented for Population 1 and Population 2 separately. For this reason, each population is discussed separately below. The eligibility criteria for mpMRI and TRUSGB in the economic model are consistent with the clinical algorithm stipulated in Section A and the Protocol.

POPULATION 1

Population 1 consists of men suspected of having prostate cancer. Of note, men who are suspected of having prostate cancer are selected if they have any of the following risk factors:

- PSA greater than 3ng/ml (or lower level if less than 50 years of age); or
- Positive family history (includes breast cancer [BRCA] gene mutation); or
- Free/total PSA ratio less than 25 per cent; or
- Positive DRE.

The PASC previously considered PSA that is “high or concerning” is a matter of clinical judgement, which involves interpreting the PSA result in relation to the patient’s age, family history, prostate volume, increase in PSA score over a 12 month period and the results of DRE examinations (Protocol p9).

The main differences in the clinical management between the intervention (mpMRI) and the comparator are:

- In the comparator arm, all patients with high or concerning PSA/DRE are referred to undergo prostate biopsy. There are no additional criteria to select patients for investigation with TRUSGB/TPUSGB.
- In the intervention arm, all patients with high or concerning PSA/DRE are referred to undergo mpMRI. Further clinical management depends on risk category (“low-concern” versus “intermediate- or high-concern”) and mpMRI results. Patients that undergo an mpMRI are split into “low-concern” or “intermediate- or high-concern” groups based on

clinical criteria using laboratory results (PSA) and family medical history. The mpMRI results are based on the PI-RADS system. Assumed clinical management for patients selected into these groups is consistent with the clinical management algorithm (Section A):

- Patients deemed “low-concern”, and assigned a PI-RADS score from 1-3 remain under observation.
- Patients deemed “low-concern”, but are assigned a PI-RADS score of 4 or 5 are referred for further investigation and undergo biopsy.
- All patients deemed “intermediate- or high-concern” are referred for further investigation and undergo biopsy.

The objective of using mpMRI in the clinical management algorithm is to improve the likelihood of a person having clinically significant PCa when undergoing prostate biopsy. The results of mpMRI contain additional diagnostic information to aid clinicians in determining the likelihood of the presence of clinically significant cancer and adjust clinical management accordingly. The PI-RADS score, which is specific for prostate imaging, provides assessment categories that summarise levels of suspicion or risk for clinically significant PCa (Weinreb et al. 2016). Patients categorised with a PI-RADS score of 4 or 5 are more likely to have clinically significant cancer and undergo biopsy to obtain confirmation of PCa. The eligibility criteria for patients undergoing mpMRI and TRUSGB for Population 1 in the economic model are consistent with the clinical algorithm stipulated in Section A and the Protocol (Figure 1 and Figure 2).

POPULATION 2

Population 2 consists of men with PCa undergoing AS. This is a sub-population of the patients from Population 1 who are diagnosed with prostate cancer. The clinical management of patients undergoing mpMRI in Population 2 is similar to the clinical management of patients undergoing mpMRI in Population 1 (Figure 3 and Figure 4).

The clinical management algorithm in the Protocol for AS and differences between the intervention and comparator groups are presented in Table 48. The differences for the arms in Population 2 occur when concerns about clinical or PSA changes occur (at any time).

Table 48 Active surveillance of men with prostate cancer

Time	Intervention	Comparator
Year 1	PSA measurement and PSA kinetics reviewed every 3-4 months; and DRE at 6-12 months.	PSA measurement and PSA kinetics reviewed every 3-4 months; and DRE at 6-12 months; and Re-biopsy after 12 months.
Years 2 to 4	PSA measurement and PSA kinetics reviewed every 3-6 months and DRE at 6-12 months	PSA measurement and PSA kinetics reviewed every 3-6 months and DRE at 6-12 months. Re-biopsy at the end of year 4
Year 5 and after	PSA measurement and PSA kinetics reviewed every 6 months and DRE at 12 months.	PSA measurement and PSA kinetics reviewed every 3-6 months and DRE at 6-12 months. Re-biopsy at the end of year 7 (and every three years thereafter)
At any time if there is concern with clinical or PSA changes	mpMRI Patients that undergo an mpMRI are split into “low risk” or “intermediate or high risk” groups based on clinical criteria using laboratory results (PSA) and family medical history. Patients deemed “low risk” and assigned a PI-RADS score between 1 to 3 return to AS. Patients deemed “low risk”, but are assigned a PI-RADS score of 4 or 5, or “intermediate or high risk” are referred for further investigation and undergo biopsy.	Re-biopsy with TRUSGB or TPUSGB.
After re-biopsy	If no evidence of disease progression, patient returns to AS; or, if evidence of disease progression, patient is offered active treatment (surgery or radiotherapy/hormone combination).	

mpMRI = multiparametric MRI, TPUSGB = trans-perineal ultrasound guided biopsy, TRUSGB = trans-rectal ultrasound guided biopsy, PSA = prostate specific antigen, DRE = digital rectal examination, PI-RADS = Prostate imaging reported and data system, AS = active surveillance.

COMPARISON OF POPULATION CHARACTERISTICS OF PATIENTS ON THE MBS

The modelled population is comparable with the expected population if mpMRI is listed on the MBS (discussed in Subsection C.2). A summary of the characteristics and circumstances of the target population, study population and wider populations that are referred for clinical management with mpMRI for Population 1 and Population 2 are presented in Table 49 and Table 50.

Table 49 Comparison of characteristics of trial and requested population and circumstances of use for Population 1, men with suspected prostate cancer

Population and circumstance	Target	Study	Wider
	As defined by the requested restriction	As defined in trials discussed in Section B	If use beyond the requested restriction might arise
Clinical condition	Men with suspected PCa with high or concerning PSA (DRE is not specified in the restriction).	Men with suspected PCa with concerning PSA and/or DRE.	Men with suspected PCa.
Comment	The wider population are larger than the target and study populations. The studies enrolled men with suspected PCa (Population 1); however, the selection criteria did not explicitly state the criteria for		

Population and circumstance	Target	Study	Wider
	As defined by the requested restriction	As defined in trials discussed in Section B	If use beyond the requested restriction might arise
	<p>high and concerning PSA for most of the key studies. The criteria for men suspected of PCa in two studies (Jambor et al. 2014; Lista et al. 2015) were PSA >4mg/ml. However, Jambor et al. (2015), excluded patients with an abnormal DRE result.</p> <p>The PASC previously considered a PSA result that is “high or concerning” is a matter of clinical judgement, which involves interpreting the PSA result in relation to the patient’s age, family history, the prostate volume, increase in PSA score over a 12 month period and the results of DRE examinations (Protocol p9).</p>		
Age	Adults (no age restriction specified)	Mean/median age range: approximately 62-70 years (Age range: 45-81 years)	Adults (no age restriction specified)
Comment	<p>Although the requested restriction does not specify eligibility based on age, the mean age at diagnosis of PCa reported in the Australian Registry studies was 66-69 years (Section C.2). This is similar to the mean/median age range of participants enrolled in the study populations. There is no expected difference in age in the wider population from the target or study populations.</p>		
Baseline risk for initiation of mpMRI	High or concerning PSA	High or concerning PSA ± negative biopsy	High or concerning PSA ± negative biopsy
Prior tests conducted	PSA	PSA/DRE and/or prior negative biopsy	PSA/DRE and/or prior negative biopsy
PSA level	Not specified.	Mean/median PSA range: approx. 4.7 to 8.3ng/mL (PSA range: 0.06-29)	Not specified.
PSA ratio/ density	Not specified.	Not reported.	Not specified.
Family history or BRCA gene positive	Not specified.	Two Australian studies (Thompson et al. 2014 and 2016) reported 26.7-30.7% of patients had family history. One study (Dikaios et al. 2015) included patients based on family history.	Not specified.
Comment	<p>The wider population may also include men who are anxious that they may have PCa, but do not fulfil the criteria of “high and concerning PSA”.</p> <p>Although not specified in the restriction, criteria for intermediate- and high-concern are specified in the clinical management algorithm: PSA >3.0ng/ml (or lower level if <50 years of age) Free/total PSA ratio <25%. Positive family history (includes BRCA gene mutation) Positive DRE</p> <p>The study population in key studies were variable: Men with prior PSA/DRE (8 out of 10 key studies). Men with prior negative biopsy (Baur et al. 2016; Lista et al. 2015). Two studies, one of which is an Australian study (Thompson et al. 2016) did not include any patients with prior biopsy (Jambor et al. 2014; Thompson et al. 2016). Seven of the key trials did not report if patients had a prior biopsy (Baldisserotto et al. 2016, Dikaios et al. 2015, Pokorny et al. 2014, Thompson et al. 2014, Wang et al. 2015, Zhao et al. 2016) Baseline prostate cancer risk in the study populations may differ from the baseline risk in the target population (see discussion in Section C.2).</p>		

Note: Study population only includes participants enrolled in the key studies.

DRE = digital rectal examination, PASC = Protocol Advisory Sub-Committee, PCa = prostate cancer, PSA = prostate specific antigen, BRCA = breast cancer.

Table 50 Comparison of characteristics of trial and requested population and circumstances of use for Population 2, men with prostate cancer undergoing active surveillance

	Target	Study	Wider
Population and circumstance	As defined by the requested restriction	As defined in trials discussed in Section B	If use beyond the requested restriction might arise
Clinical condition	Men with low to intermediate risk PCa undergoing AS.	Men low to intermediate risk PCa Gleason score ≤6, (see Section C.2)	All men with PCa undergoing AS including men with: Low to intermediate risk PCa; Clinically significant/ intermediate to high risk PCa.
Comment	The wider population is larger than the target and study populations. The target population consists of men with low to intermediate risk PCa undergoing AS (Population 2). Although high risk men are not eligible for AS with mpMRI, the wider population may include men with clinically significant/intermediate to high risk PCa undergoing AS.		
Age	Adults (no age restriction specified).	Mean/median age range: approx 61-66 years. (Age range: 45-75 years)	Adults (no age restriction specified).
Comment	Although the requested restriction does not specify eligibility based on age, the mean age of patients undergoing AS for low to intermediate risk PCa reported in the Australian Victorian Registry study was 66 years (Subsection C.2 (Weerakoon et al. 2015)). This is similar to the mean/median age range of participants enrolled in the study populations.		
Baseline risk for initiation of mpMRI	Patients with low/intermediate risk PCa undergoing AS .	Gleason score ≤6 [all key studies for all key studies, except de Cobelli et al. (2015), Gleason score was not specified]	All patients with PCa undergoing AS.
Comment	The Protocol states (p12) that the proposed mpMRI service is added to the AS protocol, and will be used as an additional test prior to biopsy. The restriction specifies the target population as men with an existing diagnosis of low or intermediate risk PCa undertaking AS, but it does not stipulate when mpMRI should be initiated. There is potential for increased use of this service in a wider population. The proposed clinical algorithm for Population 2 notes mpMRI should be undertaken if there is concern about clinical or PSA changes. However, the restriction does not explicitly state these time points when mpMRI would be performed.		
Tests conducted	Not explicitly specified. Restriction notes that the person should be undertaking AS. No other information is provided.	PSA/DRE and biopsy. Other tests noted include PHI and PCA3 (Porpiglia et al. 2015).	Assumed in clinical management due to definitive PCa diagnosis : PSA, and PSA kinetics, DRE, TRUSGB .
Comment	The target and wider populations are broader than the study populations. The restriction requested for the target population specifies 'man has existing diagnosis of low or intermediate risk PCa and is undertaking AS. The wider population may include patients who have clinically significant/intermediate to high risk PCa.		
Limitation on frequency use	Not specified.	Not specified.	Not specified.
Comment	The restriction does not specify if there is a limitation on frequency of use in the target population.		

Study population only includes participants enrolled in the key studies.

AS = active surveillance, DRE = digital rectal examination, mpMRI = multiparametric MRI, PCa = prostate cancer, PSA = prostate specific antigen, TPUSGB = trans-perineal ultrasound guided biopsy, TRUSGB = trans-rectal ultrasound guided biopsy.

D.3. STRUCTURE AND RATIONALE OF THE ECONOMIC EVALUATION

A summary of the key characteristics of the economic evaluation is given in Table 51. The economic model is a combined decision tree and Markov model using cohort expected value analysis. One economic model is presented which includes both Population 1 and Population 2.

Table 51 Summary of the economic evaluation

Perspective	MBS perspective
Comparator	TRUSGB/TPUSGB
Type of economic evaluation	Cost-utility analysis
Sources of evidence	Systematic review and meta-analysis of clinical trials (presented in Section B) Targeted review for utility parameters (Section C) Expert opinion was elicited where no data were available
Time horizon	Lifetime time horizon (25 years) in the model base-case
Outcomes	QALYG
Methods used to generate results	Combined decision tree and Markov model using cohort expected value analysis
Health states	No prostate cancer Low to intermediate risk prostate cancer (insignificant cancer) Intermediate to high risk prostate cancer (significant cancer) Advanced prostate cancer Death
Cycle length	1 year
Discount rate	5% for costs and outcomes
Software packages used	TreeAge Pro 2015

MBS = medical benefits scheme, TRUSGB = trans-rectal ultrasound guided biopsy, TPUSGB = trans-perineal ultrasound guided biopsy, QALYG = quality of life-years gained.

LITERATURE REVIEW

Two searches were conducted to identify any studies of economic evaluations that may be relevant to this evaluation. Studies included for detailed review were those that were based on:

- Economic evaluations using a model to assess costs, cost-effectiveness or cost-utility of mpMRI or TRUSGB/TPUSGB; and
- Populations including:
 1. Men suspected or prostate cancer (Population 1); and/or
 2. Men with low to intermediate risk prostate cancer under AS (Population 2).

The use of mpMRI for PCa screening is relatively new and studies that assess the cost-effectiveness or cost-utility are recent. The first search included a review of websites of key health technology assessment agencies. A second search was conducted in the PubMed database with an aim to identify any economic evaluations of mpMRI. Details of the search strategy are presented in Appendix K. The bibliographies of all retrieved studies were manually reviewed to identify all relevant studies.

From the search of key HTA websites, two agencies that have reviewed cost-effectiveness of mpMRI or TRUSGB were identified:

- CADTH: The report identified on the CADTH website did not explicitly include mpMRI, but did include TRUSG (CADTH 2014) B. The rapid response report from CADTH noted that there were no economic evaluations identified in the literature that compared the cost-effectiveness of magnetic resonance spectroscopic imaging versus TRUSGB for prostate disease diagnosis in men aged 50 years and older.
- NICE: The clinical guidelines for prostate cancer: diagnosis and management (NICE 2014) have recommended to consider mpMRI in men with a negative TRUSGB to determine if another biopsy is needed. Noting that the basis for this recommendation was not substantiated in this guideline.

No studies were identified that assessed the cost-effectiveness or cost-utility of mpMRI alone compared with TRUSGB or TPUSGB in either Population 1 or Population 2. The economic evaluations pertaining to mpMRI identified reviewed the clinical management sequence of mpMRI followed by MRIGB. Although this contracted assessment is specific for mpMRI since MRIGB is being assessed separately (CA 1424), the studies were retained as the clinical algorithm and model structure presented in this assessment (CA 1397) follow the sequence of mpMRI followed by biopsy.

Gordon et al. (2016) evaluated the cost-effectiveness of two mpMRI strategies compared with usual care (TRUSGB or TPUSGB) (Gordon et al. 2016). This economic evaluation does meet the criteria for inclusion and has been retained for further review. Results from this economic evaluation (CA 1397) are compared with the evaluation conducted by Gordon et al. (2016) (Subsection D3). Authors from this publication are also part of the assessment group that are conducting the evaluation for MRIGB (CA 1424).

All the identified economic models included a comparison of the technologies in men with suspected PCa. There were no economic models comparing mpMRI ± TRUSGB or TPUSGB or MRIGB with TRUSGB/TPUSGB, where the preliminary health state comprised of men with low to intermediate risk PCa. There were six studies of interest identified (Cerantola et al. 2016; de Rooij et al. 2014; Gordon et al. 2016; Hutchinson et al. 2016; Lotan et al. 2015; Mowatt et al. 2013) that performed an economic evaluation of mpMRI plus prostate biopsy (MRIGB or TRUSGB) compared with TRUSGB in

men suspected of prostate cancer. One publication by (Nicholson et al. 2015) used mpMRI and/or MRIGB as part of a mixed comparator arm.

The models described in the literature did not completely match the criteria for this submission on review of the full text and a rationale for their exclusion is presented in Table 52. However, a summary of these economic evaluations is detailed in Table 53.

Table 52 Grounds for not using a published economic evaluation in the current assessment

Trial ID	Grounds for not using model
Gordon et al. (2016)	The results in the model are specific for Population 1, however, cost-effectiveness in Population 2 are not reported.
Cerantola et al. (2016)	The perspective in the evaluation (Canadian Provincial public health system) is not applicable to the Australian population.
Lotan et al. (2015)	The evaluation presented in this publication is a cost-analysis and does not provide a full economic evaluation. The population is a subset of the target population requested by this submission i.e. only men with a prior negative biopsy. Population 2 is not included in the evaluation.
Nicholson et al. (2015)	The economic evaluation compares different diagnostic tests from this evaluation. It is a cost-effectiveness analysis of: PCA3 score or phi in combination with existing tests; Existing tests (including histopathology results, PSA level and DRE), mpMRI and clinical judgement. The population is a subset of the target population requested by this submission i.e. only men with a prior negative biopsy in men with suspected PCa.
de Rooij et al. (2014)	The perspective in the evaluation (i.e. Dutch healthcare perspective) is not applicable to the Australian population.
Mowatt et al. (2013)	A different decision problem is addressed: The use of different forms of mpMRI, including T2-MRI, to inform the location of a second biopsy rather than to inform whether or not a biopsy should be undertaken (Nicholson 2015).

DRE = digital rectal examination, mpMRI = multiparametric MRI, PCa = prostate cancer, PCA3 = prostate cancer gene 3, PSA = prostate specific antigen; PSA = prostate specific antigen.

Table 53 Summary economic evaluations identified in the literature

	Gordon et al. (2016)	Cerantola et al. (2016)	Lotan et al. (2015)	Nicholson et al. (2015)	de Rooij et al. (2014)	Mowatt et al. (2013)
Perspective	Health care system (Australia) and out of pocket costs for patients.	Health care system (Canada) [Provincial public health system]	Not explicitly reported. (USA) [-societal]	Healthcare perspective [UK, NHS]	Healthcare perspective [The Netherlands]	Healthcare perspective [UK, NHS]
Population	<i>Population 1</i> Men with suspected PCa who have not had a prior biopsy.	<i>Population 1</i> Biopsy naïve men with clinical suspicion of PCa based on DRE and PSA > 4-10ng/ml. <i>Note: Population 2 are modelled, but are not the baseline cohort.</i>	<i>Population 1</i> Men with prior negative biopsy	<i>Population 1</i> Men with suspected PCa with prior negative or equivocal biopsy	<i>Population 1</i> Men with elevated PSA (>4ng/mL) who never had a prostate biopsy	<i>Population 1</i> Men with prior negative biopsy
Interventions	Strategy 2: mpMRI ± MRIGB Strategy 3: mpMRI ± (MRIGB or TRUSGB or TPUSGB)	MRIGB [mpMRI + MRIGB]	mpMRI with biopsy TRUSGB	PCA3 score or phi in combination with existing tests [comparators as below]	mpMRI + MRIGB	MRS/MRI sequences to direct TRUSGB
Comparator	Strategy 1: TRUSGB	TRUSGB (12-core)	TRUSGB	clinical assessment clinical assessment and MRI <i>mpMRI and MRIGB is part of clinical assessment.</i>	TRUSGB	Extended TRUSGB
Type of economic evaluation	CEA and CUA	CUA	Cost analysis	CEA and CUA	CUA	Cost analysis, CEA and CUA
Sources of evidence	Systematic literature review	Literature [unclear if review was systematic]; base assumptions were made by authors and expert opinion.	Systematic literature review	Systematic literature review	Systematic literature searches, meta-analyses, and expert opinion	Systematic literature searches, meta-analyses, indirect comparison, and expert opinion.

	Gordon et al. (2016)	Cerantola et al. (2016)	Lotan et al. (2015)	Nicholson et al. (2015)	de Rooij et al. (2014)	Mowatt et al. (2013)
Time horizon	Lifetime: ~30 years, max. age is when age 90 is reached unless they die earlier.	5, 10, 15 and 20 years	not stated	Base-case: 3 years Sensitivity: 1 and 6 years	10 years over initial suspicion of PCa [after this time no differences was assumed]	Lifetime: ~30 years Sensitivity: shorter time horizons
Outcomes	No. of biopsies Costs LYs QALYs	Costs QALYs	Costs No. of biopsies No. cancers detected	Costs LYs QALYs	Costs QALYs	Costs LYs QALYs
Methods used to generate results	Markov model using cohort expected value analysis	Markov model with Monte Carlo microsimulations	Decision tree model	Decision tree	Combined decision tree and Markov model	Markov model
Health states	The PCa base model consisted of 17 health states (Markov model) ^a <i>The PCa base model was altered to address cost-effectiveness for mpMRI strategies compared with TRUSGB, and included additional health states (n=3):</i> Biopsy naïve; PCa negative, missed PCa; PCa negative, PSA monitor.	10 health states MRIGB (mpMRI) or Biopsy positive (TRUSGB); Follow up; LR PCa; I-HR PCa; AS; treatment; relapse; CRPC; Death PCa; Death, all causes.	Not applicable	Not applicable	2 health states: alive and dead.	7 basic states: (1) no or undetectable cancer; (2) localised (T1–T2) PC (low risk); (3) localised PC (intermediate risk); (4) localised PC (high risk); (5) locally advanced cancer (T3); (6) metastatic cancer; and (7) PC death.
Cycle length	1 year	1 year	not applicable	not applicable	1 year	3 months
Currency and year	2015 AUD \$	2014 CAD \$	2014 USD \$	2012/13 GBP £	[Year, NR] EUR €	2009/10 GBP £
Discount rate	5% (costs and benefits)	5% (costs and benefits)	Not stated	3.5% pa (costs and benefits)	Costs 4% Benefits: QALYs 1.5%	3.5% pa (costs and benefits)
Software packages used	TreeAge Pro 2015	TreeAge Pro 2013	TreeAge Pro [year not stated]	Not stated	TreeAge Pro 2012	Not stated.
Base-case result	The mpMRI (Strategies 2 and 3) were marginally inferior to	MRIGB was the dominant strategy	[PCa prevalence 24%] TRUSBx: \$90,400	Clinical assessment + MRI costs less but is	€323 / QALYG Assuming MRIGB:	Discounted lifetime costs:

	Gordon et al. (2016)	Cerantola et al. (2016)	Lotan et al. (2015)	Nicholson et al. (2015)	de Rooij et al. (2014)	Mowatt et al. (2013)
	TRUSGB (Strategy 1) [base-case results are presented in Gordon et al 2016 Table 12 p33]	over 5, 10, 15 and 20 years in the base-case.	mpMRI: \$87,700 The MRI arm detected fewer cancers (16 vs. 20.4), while 73 biopsies were avoided.	less effective than: clinical assessment + MRI + PCA3 £5,418,366/QALYG clinical assessment + MRI + PHI: £2,500,530/QALYG <i>Other results:</i> <i>mpMRI is not cost-effective compared with clinical assessment alone (p134).</i>	100% specificity 90% sensitivity	TRUSGB: £3895 T2-MRI or DCE-MRI: £4056

^a: In Gordon et al. (2016), the base model consisted of 17 health states separated into initial health states, subsequent health states after the first year of diagnosis, and health states describing are treatment options after the first year of diagnosis. *Initial Health States (n=4)*: Very low and low risk (T1-T2a, Gl ≤6, PSA<10ng/ml); Intermediate risk (T2b-T2c, Gl 7, PSA 10-20ng/ml); High risk to locally advanced (T3-T4, Gl 8-10, PSA >20ng/ml); Advanced disease (node positive, metastatic); *Subsequent HS (n=8) after first year of diagnosis*: Post surgery (LR); Post surgery (IHR); Post radiation as 1st-line (LR); Post radiation as 1st-line (IHR); Post ADT+radiation; Post surgery + radiation; Post 1st-line chemotherapy; and Post 2nd-line chemotherapy; *HS describes care after the after first year of treatment (n=5)*: Castrate-resistant prostate cancer; Active surveillance; Watchful waiting; Palliative care; Death.

ADT = androgen deprivation therapy, CAD = Canadian dollars, CEA = cost effectiveness analysis, CRPC = castrate resistant prostate cancer, CUA = cost utility analysis, DCE= dynamic-contrast enhanced, DRE = digital rectal examination, EUR = Euros, GBP = Great British pound, HS = health state, IHR = intermediate to high risk, LR = low risk, LY = Life years, mpMRI = multiparametric MRI, MRIGB = magnetic resonance guided biopsy, MRI = magnetic resonance imaging, NHS = National Health System, NR = not reported, PCa = prostate cancer, PCA3 = prostate cancer gene 3, PHI = prostate health index, PSA = prostate specific antigen, QALY = Quality adjusted life year, QALYG = Quality adjusted life year gained, TPUSGB = trans-perineal ultrasound guided biopsy, TRUSGB = trans-rectal ultrasound guided biopsy, USD = United States Dollars.

STRUCTURE OF THE ECONOMIC EVALUATION

A combined decision tree and Markov model and was used in this evaluation (TreeAge 2015). Cohort expected value analyses were performed for an average male patient (starting age 66 years).

An Australian health care perspective was taken. A discount rate of 5% was applied to costs and outcomes. Results without discounting are presented in a sensitivity analysis.

The decision analysis compares the use of mpMRI (+ biopsy for a proportion of patients) with biopsy for all. The Markov structure includes five health states, “no cancer”, “low to intermediate risk cancer (active surveillance)”, “intermediate to high risk cancer”, “advanced cancer” and “death”. A cycle length of 1-year was applied, without half cycle correction. The impact of including a half cycle correction was tested in a sensitivity analysis (see Subsection D.6). In each cycle subjects may transition through health states, however subjects cannot transition back from:

- “low to intermediate risk cancer” or “intermediate to high risk cancer” to “no cancer”; or
- “intermediate to high risk cancer” to “low to intermediate risk cancer”; or
- “Advanced prostate cancer” to “intermediate to high risk cancer” to “low to intermediate risk cancer”; or
- “death”, subjects remain in this state.

All subjects enter the model as “men suspected of having prostate cancer” (Population 1) in the decision tree portion of the model. Men in the “low to intermediate risk cancer” health state are assumed to undergo AS (Population 2).

Descriptions of each of the health states are as follows:

- The “no cancer” health state describes patients that have not been diagnosed with prostate cancer.
- The “low to intermediate risk cancer” health state describes men with PCa undertaking active surveillance and consists of patients in Population 2.
- The “intermediate to high risk cancer” health state includes men with intermediate to high risk PCa undertaking active treatment and follow-up. These patients are followed up indefinitely.
- The “advanced prostate cancer” health state includes men undertaking active treatment and follow up. These patients are followed up indefinitely.
- The “death” state is an absorbing health state and includes all patients who have died.

Costs and health effects are assigned for each health state. Disutilities associated with biopsy procedures and treatment complications are applied as decrements. A description of the interventions being compared, outcomes and costs included are presented in Subsection D.4. Utility values are presented in Subsection C.4.

As PCa grows slowly (AIHW 2013), a cycle length of one year and a lifetime time horizon (25 years) is used in the model. This is consistent with the assessment for MRIGB (CA 1424) and with other recent economic evaluations identified in the literature (Cerantola et al. 2016; de Rooij et al. 2014).

The structure of the economic model is shown in Figure 13 (Population 1, mpMRI), Figure 14 (Population 1, TRUSGB), Figure 15 (Population 2, mpMRI), Figure 16 (Population 2, TRUSGB) and Figure 17 (Population 1 and 2, markov structure).

Figure 13 Population 1: mpMRI

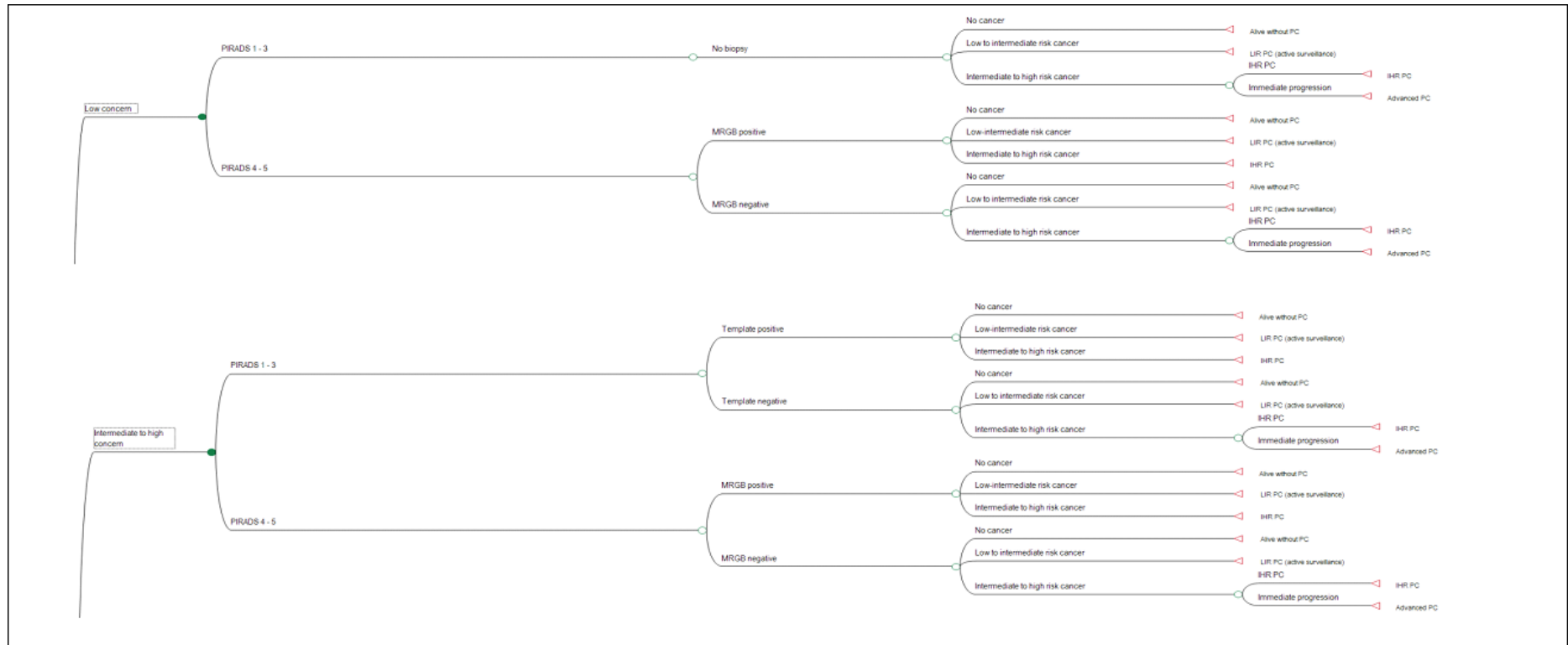


Figure 14 Population 1: TRUSGB

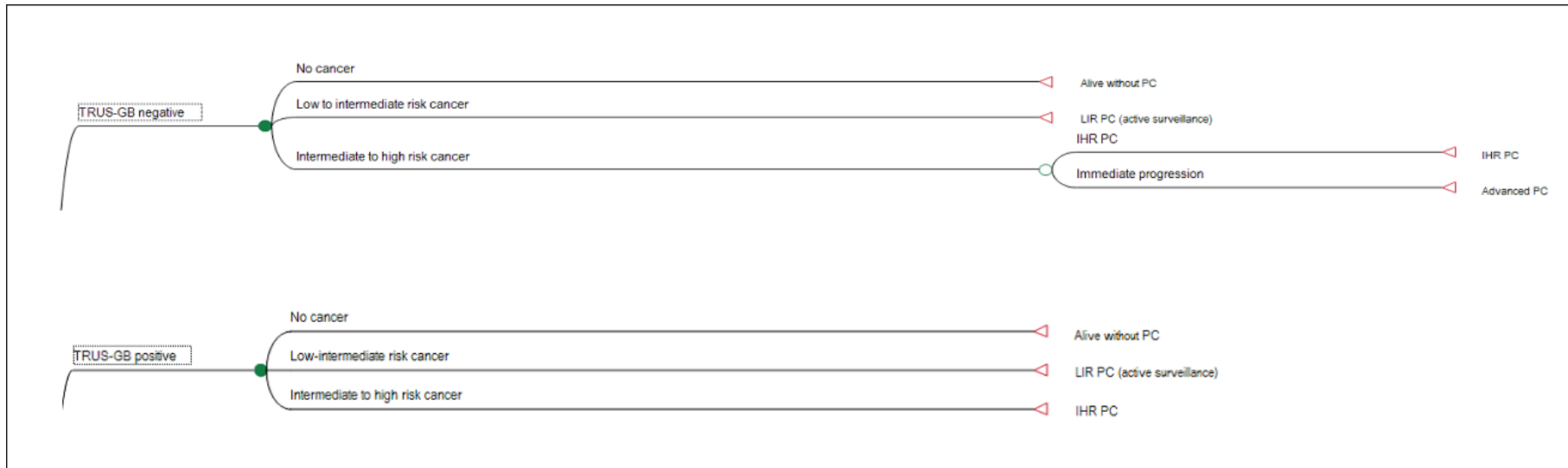


Figure 15 Population 2: mpMRI

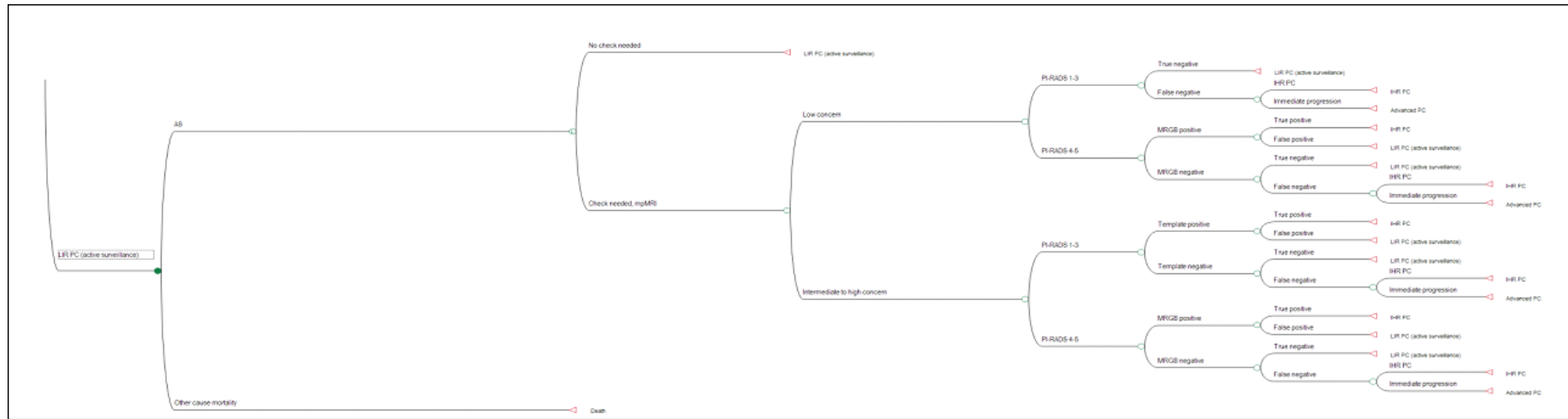


Figure 16 Population 2: TRUSGB

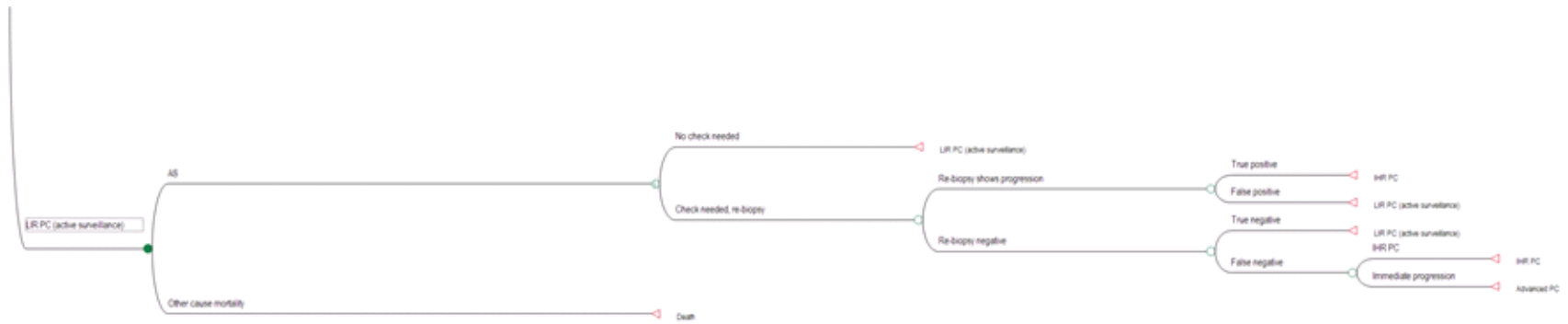
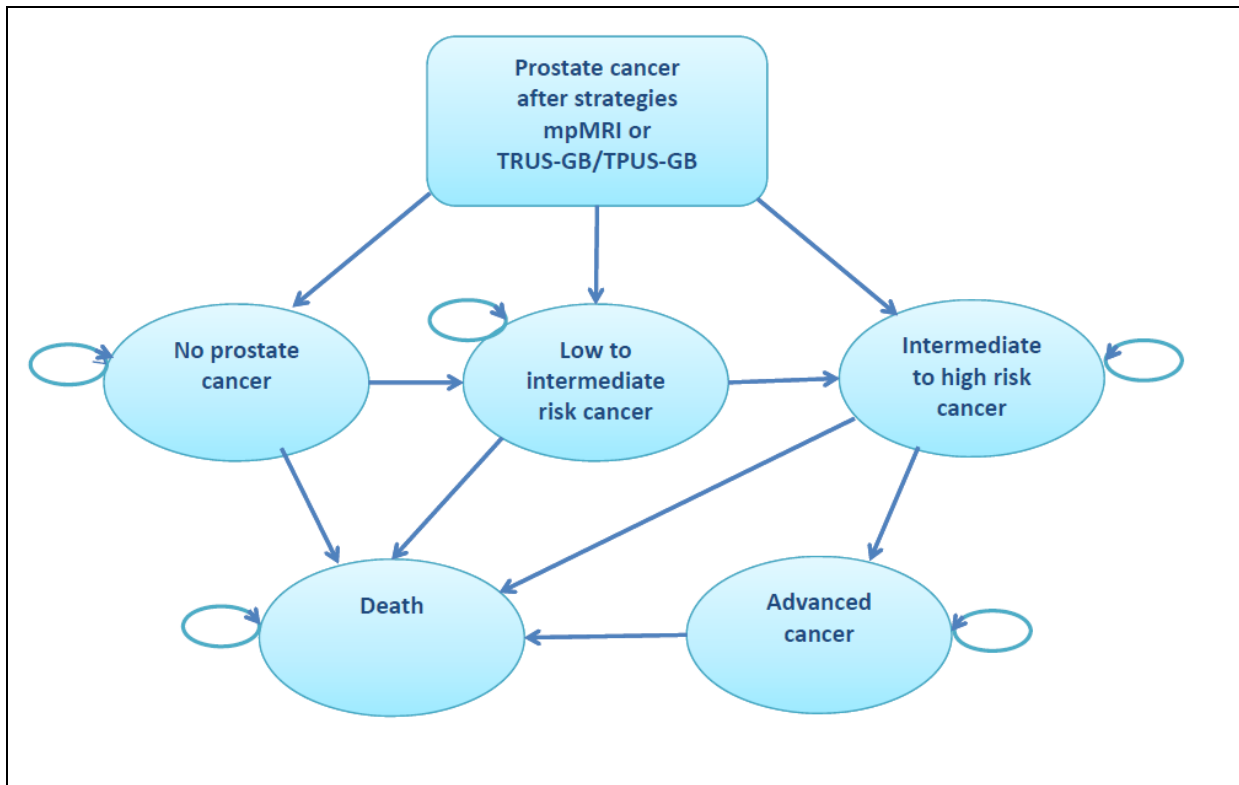


Figure 17 Markov transition states



A comparison of the economic model presented in this assessment (CA 1397) and the economic model presented by Gordon et al. (2016) is provided in Table 54. The main differences between the models are the number of health states and perspectives presented. The economic evaluation presented by Gordon et al. (2016) presented 20 health states (17 health states for patients with PCa, and 3 additional states for patients undergoing screening) and in this assessment 5 health states are presented. Gordon et al. (2016) included out-of-pocket costs for patients, whereas this assessment only takes the perspective of the MBS. The key structural assumptions are the same; mean age of the cohort is 65-66 years, time horizon applied for a lifetime up to age 90 years, costs and benefits are discounted at 5 per cent.

Table 54 Comparison of key economic evaluations: CA 1397 and Gordon et al. (2016)

	CA 1397	Gordon et al. 2016
Perspective	MBS, health care system (Australia)	Health care system (Australia); Out of pocket costs for patients.
Population	<i>Population 1</i> Men with suspected PCa. <i>Population 2</i> Men with low to intermediate risk PCa in AS.	<i>Population 1</i> Men with suspected PCa who have not had a prior biopsy.
Interventions	mpMRI ± TRUSGB/TPUSGB [75%:25%]	Strategy 2: mpMRI ± MRIGB Strategy 3: mpMRI ± (MRIGB or TRUSGB or

	CA 1397	Gordon et al. 2016
		TPUSGB) [33.3% of each type of biopsy]
Comparator	TRUSGB/TPUSGB	Strategy 1: TRUSGB
Type of economic evaluation	CEA and CUA	CEA and CUA
Sources of evidence	Systematic review and meta-analysis of clinical trials (presented in Section B)	Systematic literature review
Time horizon	Lifetime time horizon (25 years) in the model base-case	Lifetime: ~30 years, maximum is when men reach age 90 unless they die earlier.
Outcomes	No. of biopsies Costs QALYs	No. of biopsies Costs LYs QALYs
Methods used to generate results	Combined decision tree and Markov model using cohort expected value analysis	Markov model using cohort expected value analysis
Health states	No prostate cancer Low to intermediate risk prostate cancer (insignificant cancer) Intermediate to high risk prostate cancer (significant cancer) Advanced prostate cancer Death	The base model consisted of 17 health states (Markov model), which was altered to address research question and included additional health states (n=3): Biopsy naïve; PCa negative, missed PCa [false negatives]; PCa negative, PSA monitor [true negatives]. Men enter the base model when PCa is detected.
Cycle length	1 year, half-cycle correction only applied in a sensitivity analysis	1 year, half cycle correction applied in the base-case.
Currency and year	2014 AUD \$	2015 AUD \$
Discount rate	5% (costs and benefits)	5% (costs and benefits)

MBS = medical benefits scheme, mpMRI = multiparametric MRI, MRIGB = MRI guided biopsy, TRUSGB = trans-rectal ultrasound guided biopsy, TPUSGB = trans-perineal ultrasound guided biopsy, CEA = cost-effectiveness analysis, CUA = cost-utility analysis, QALY = quality of life-years, AUD = Australian dollar, LY = life years, PCa = prostate cancer.

ASSUMPTIONS INCORPORATED INTO THE MODEL STRUCTURE

In estimating the costs and outcomes of mpMRI ± prostate biopsy compared with prostate biopsy, several assumptions were made:

- All patients enter the model at age 66, which is the mean age of PCa diagnosis in Australia. Over time patients that have entered the model will age, and their background mortality (obtained from ABS statistics) will change accordingly.
- All patients enter the model as men with suspected PCa (Population 1). Patients that are entering Population 2, men with low or intermediate risk prostate cancer undergoing AS, are a subset of what previously used to be Population 1.

- A cost associated with delayed diagnosis is applied for patients with false negative results. Delayed diagnosis was assumed not to impact PCa prognosis (see Subsection C.3).
- Patients with false positive results have the same prognosis as other patients without cancer, but were assumed to spend a year under “active surveillance” (like low/intermediate risk prostate cancer patients).
- Patients may remain in any health state or progress, but may not regress.
- The introduction of mpMRI does not alter the rest of the clinical treatment algorithm, i.e. the types of biopsies used remain the same. For the base-case, a weighted average of the various types of biopsy is assumed (TRUSGB, 75%; and TPUSGB 25%). This assumption is made as MRIGB is currently not available on the MBS. The use of MRIGB was included in a sensitivity analysis. Accuracy of MRIGB was aligned with the assessment being conducted for MRIGB (CA 1424).
- Patients are managed according to the clinical algorithms presented in Section A.

D.4. INPUTS TO THE ECONOMIC EVALUATION

The variables in the economic evaluation are presented in the following categories:

- Transition probabilities
- Complications associated with biopsy, and treatment related AEs
- Costs
- Utility values.

TRANSITION PROBABILITIES

Probabilities in the decision tree were dependent on test accuracy. The key accuracy inputs in the model are the sensitivity and specificity of mpMRI and prostate biopsy. Test accuracy information for mpMRI was obtained from Section B.3.6. Gordon et al. (2016) obtained test accuracy of mpMRI from a meta-analysis by de Rooji et al. (2014) (sensitivity 76%, specificity 86%). The estimate for sensitivity from de Rooji et al. (2014) is similar to the base-case estimate in this assessment, but higher than the estimate from the pooled Australian studies; and the estimate for specificity is higher than the base-case in this assessment, but similar to the pooled Australian estimate.

Test accuracy information for the various types of biopsies was aligned with the group conducting the assessment for MRIGB (CA 1424). All accuracy inputs are presented in Table 55. In the base-case, 75 per cent of the prostate biopsies were assumed to be TRUSGB and 25 per cent of the prostate biopsies were assumed to be TPUSGB. Accuracy of TPUSGB was assumed to be equal to TRUSGB.

Given that MRIGB for prostate cancer diagnosis is not currently listed on the MBS, the impact of using this type of biopsy on the cost-utility of mpMRI was evaluated in a sensitivity analysis in Section D.6.

Table 55 Test accuracy of mpMRI, TRUSGB/TPUSGB and MRIGB

Description	Sensitivity, mean [95%CI]	Specificity, mean [95%CI]	Source	Used in
mpMRI	73.4% [57%, 85%]	77.1% [63.5%, 86.7%]	Section B.3.6	Base-case
mpMRI (Australian studies only) ^a	54.3% [38.3%, 69.5%]	87.2% [74.8%, 94.0%]	Section C.2	Sensitivity analysis B
TRUSGB	81% [70%, 88%]	93.64% [89.4%, 96.3%]	Schoots et al. 2015 Table 3; Pokorny et al. (2014) Table 5	Base-case
TPUSGB	81% [70%, 88%]	93.64% [89.4%, 96.3%]	Assumed equal to TRUSGB	Base-case
MRIGB ^b	85% [80%, 89%]	96.91% [93.4%, 98.6%]	Schoots et al. (2015) Table 3; Pokorny et al. (2014) Table 5	Sensitivity analysis A

^a: Australian studies include, Pokorny et al. (2014), Thompson et al. (2014) and Thompson et al. (2016).

^b: Accuracy measures for MRIGB were provided by the assessment group (CA 1424).

CI = confidence interval, mpMRI = multiparametric MRI, MRIGB = magnetic resonance guided biopsy, TPUSGB = trans-perineal ultrasound guided biopsy, TRUSGB = trans-rectal ultrasound guided biopsy.

To calculate the probabilities associated with each of the branches in the decision tree, the following formulas were used:

- Probability of a positive test = sensitivity*prevalence + (1-specificity)*(1-prevalence).
- Positive predictive value = sensitivity*prevalence / sensitivity*prevalence + (1-specificity)*(1-prevalence).
- Probability of a negative test = (1-sensitivity)*prevalence + specificity*(1-prevalence).
- Negative predictive value = specificity * (1-prevalence) / (1-sensitivity)*prevalence + specificity*(1-prevalence).

Prevalence of prostate cancer in Population 1 was assumed to be 35 per cent for low-concern patients and 50per cent for intermediate- to high-concern patients, consistent with advice from the applicant (Applicant 2016). The prevalence of progressed (significant) cancer in patients undergoing re-biopsy as part of AS was assumed to be 15 per cent, to reflect a proportion of ~8.8% of men (Simpkin et al. 2015) moving from AS to radical treatment per year, under the current clinical algorithm (assuming sensitivity of re-biopsy is 0.81 and specificity is 0.94). Approximately 50 per cent of the patients were assumed to be of low-concern versus intermediate- to high-concern. The overall proportion of cancers that was assumed to be of low to intermediate risk (insignificant) as opposed to intermediate to high risk (significant) was assumed to be 90 per cent in the low-concern patients and 10 per cent in the intermediate- to high-concern patients.

Transition probabilities used by Gordon et al. (2016) were stratified by the sensitivity and specificity of the biopsy type by cancer risk (see Table 11 pp31-32 in Gordon et al. 2016). This assessment assumed that sensitivity and specificity for biopsy was the same for low risk and intermediate to high risk prostate cancer.

ADVERSE EVENTS

Adverse events contribute to total medical costs and affect quality of life. Only AEs that occur frequently and have serious impacts on quality of life and/or resource utilisation were included. The AEs resultant from prostate biopsy and PCa treatment included in the economic model include: sepsis (biopsy related), erectile dysfunction (treatment related), and urinary incontinence (treatment related). Cost and utility decrements for sepsis are applied to all biopsies. Cost and utility decrements for erectile dysfunction and urinary incontinence are applied in the “intermediate to high risk” health state. The probabilities and rates of treatment related AEs in the model are obtained from the NSW Cancer Registry (Smith et al. 2009) and Gordon et al. (2016).

Consistent with the assessment of MRIGB (CA 1424), the cost for biopsy-related sepsis was assumed to be \$4,527 (AR-DRG T61B, post-operative infection, from NHCDC 2013-14, Round 18). The costs of treatment-related AEs are included in the total costs of treated PCa patients obtained from the literature (Cronin et al 2016), see the “costs” section below. The frequencies of the AEs are presented in Table 56. The sources of the frequency of adverse events in this assessment are the same as that presented by Gordon et al. (2016). The probabilities have been weighted assuming 50 per cent of patients are treated by radical prostatectomy and 50 per cent by radiotherapy.

Table 56 Frequency of adverse events associated with biopsy and treatment of prostate cancer.

	Rate	Probability	Note and source
Biopsy related AEs			
Sepsis from infection	1.2%	NA	Applied to all biopsy measures (consistent with CA 1424); Leahy et al. (2015)
Treatment related complications in “intermediate to high risk” health state			
Erectile dysfunction	NA	0.415	Weighted probability (50/50): (50% RP+ 33% EBRT) / 2 = 41.5%; NSW Cancer Registry (Smith et al. (2009); Gordon et al. (2016))
Urinary incontinence	NA	0.062	Weighted probability (50/50): (10% RP+ 2.4% EBRT) / 2 = 6.2 %; NSW Cancer Registry (Smith et al. (2009); Gordon et al. (2016))

AE = adverse event, EBRT = external beam radiotherapy, NA = not applicable, RP = radical prostatectomy.

COSTS

In the economic evaluation, costs were estimated by multiplying the quantity of consumed healthcare resources with their associated unit costs. Resource consumption was based on clinical guidelines and the treatment algorithms provided in the assessment Protocol. Unit costs were determined based on MBS fees for medical procedures. To specify these in Section E, costs for

medical procedures were obtained with and without co-payments. All costs were reported in Australian dollars from the year 2014. Where costs were obtained from previous years, they were inflated using the Health CPI (Australian Institute of Health and Welfare 2015). Table 59 provides an overview of all costs included in the economic evaluation. Further explanation about the various cost items is provided below.

The intervention: mpMRI scan of the prostate

The Protocol states the current fee charged for mpMRI is \$600, both for men suspected of having PCa and men under AS for PCa (DoH 2016a). PASC noted that the cost for the contrast agent was included in these proposed fees. PASC suggested that the cost of the contrast agent should be listed separately, as for other MRI items. The MBS item for the use of contrast for MRI (item 63491) has a fee of \$44.80, therefore, subtracting the cost of contrast from the proposed fee (\$600.00-\$44.80) results in a fee of \$555.20 for mpMRI of the prostate.

This fee (\$555.20) is higher than the current MBS fees for similar procedures. For example, the fee for MBS item 63476 (MRI for the initial staging of rectal cancer) is \$403.20, which is \$152 lower. It is not clear from the Protocol if there is a rationale for a higher fee for mpMRI of the prostate. In the economic evaluation, 85 per cent of the proposed fee was used, to reflect the MBS part of the costs (excluding co-payments). Given a cost of \$555.20 for mpMRI plus \$44.80 for contrast, the modelled cost was \$510. This fee was reduced, and a sensitivity analysis performed using a cost of \$448 (\$403.20 for mpMRI plus \$44.80 for contrast).

Costs for buscopan to limit bowel peristalsis and costs for oral medication for patients with claustrophobia were excluded since their impact would be negligible given the low price of these drugs. The proportion of patients requiring sedation due to severe claustrophobia was also considered to be negligible since it is an uncommon condition and urologists likely prefer not to use mpMRI for screening/surveillance purposes in these patients. Costs for intravenous access disposables were assumed to be included in the MBS fee for contrast enhancement.

The cost of mpMRI used by Gordon et al. (2016) was lower at \$570. The source used in this study was Protocol CA 1397; however, the current Protocol notes the current fee charged including contrast is \$600.00.

Prostate biopsy

The costs for biopsy procedures were aligned with the evaluation of MRIGB procedures for diagnosis of PCa (CA 1424). For TRUSGB these costs (85% MBS fees) included the biopsy procedure (MBS item 37219), prostate ultrasound (MBS item 55600), biopsy specimen analysis (MBS item 72825) and antibiotic prophylaxis (ciprofloxacin, PBS item 1209P). For TPUSGB these costs (85% MBS fees) included the biopsy procedure (MBS item 37219), prostate ultrasound (MBS item 55600), biopsy specimen analysis (MBS item 72825), general anaesthesia (MBS items 17615 and 23051) and the

admission theatre (National Efficient Price (NEP)), price weight subacute minor surgical), see CA 1424. The relative utilisation of TRUSGB versus TPUSGB was assumed to be 75:25 (see Protocol 1424), resulting in cost of \$603.92 per prostate biopsy. This cost is similar to that used in Gordon et al. (2016) where \$600.00 per biopsy was assumed.

Costs for observation

Patients in the health state “alive without prostate cancer” were assumed to undergo PSA testing once per year, costing \$31.75 (85% MBS fee for item 66659).

Prostate cancer costs

Prostate cancer costs for the economic evaluation were sourced from literature. A targeted literature review was performed to identify studies reporting the treatment costs of patients with PCa from the Australian healthcare system perspective (see Appendix K). One study was selected for inclusion as the authors reported costs from the Australian healthcare system perspective (Cronin et al. 2016). This study used individual patient data for the derivation of costs. Other costs not reported in the studies were sourced from Protocols 1397 and 1424.

Prostate cancer costs, healthcare payer perspective

Cronin et al. (2016) reported the long-term health costs associated with PCa in an Australian population. The study was conducted from the healthcare payer perspective and included medical, pharmaceutical and hospital usage costs from the Pharmaceutical Benefits Scheme (PBS), Medicare Benefit Schedule (MBS), and hospital utilisation. Details of the study are presented in Table 57. Costs from this study were used as they included an aggregate cost of each of the treatments associated with the intermediate to high risk health state in the economic model. Resource utilisation was measured over a long period of follow-up (10 years). The study used real-world, linked data for individual patients to calculate PCa costs, and is therefore considered more comprehensive than forecasting PCa costs based on expected resource utilisation.

Table 57 Summary of cost study by Cronin et al (2016)

Study details	
Study design	Analysis of linked medical, pharmaceutical and hospital data.
Population	Males (aged <70) diagnosed with PCa in the years between 2000 and 2002 (n=1,873).
Location	NSW, Australia.
Time of conduct	Data pertains to patients diagnosed in the years 2000 and 2002, and includes 10 years of follow-up Costs were inflated to common price year (2011/2012) using the AIHW pharmaceutical services fee index or medical services index.
Objectives	To estimate the long term health care costs of PCa.
Methods	Non-parametric models were used to calculate the average health care costs by PCa risk groups at

Study details	
Variables included	<p>diagnosis (low to metastatic) and treatment pathways.</p> <p>Data pertaining to disease stage and treatments received were extracted from patient medical records. PCa pharmaceuticals were defined as those currently approved on the PBS for PCa related indications. General pharmaceuticals were included if they were considered to be related to the treatment of PCa.</p> <p>Medical services: PCa relevant MBS item numbers in combination with the MBS descriptor 'provider specialty'. PCa specific provider specialties included medical oncology, diagnostic radiology, immunology, urology and radiation oncology; if it were not possible to distinguish between services utilised for PCa and non-PCa, general services were matched to PCa relevant procedures if they occurred within a 3 days of a PSA/urinary test, or at the same hospital visit.</p> <p>Hospital usage: Australian Refined Diagnostic Related Groups (AR-DRG) were linked to prostate related ICD-10 diagnostic codes and categorised as major and general prostate procedures, gastrointestinal, urinary and penile and metastases (including chemotherapy and hospital related admissions).</p>
Outcomes	Average health care costs by PCa risk groups at diagnosis (low to metastatic) and treatment pathways.
Key findings and conclusions	<p>The initial phase of treatment is associated with the highest costs of care for all treatment groups. Ongoing costs for all treatments show a declining trend after the first six months post diagnosis with the exception of radical prostatectomy ±EBRT, and EBRT± brachytherapy, which shows a small second spike in costs between 30-42 months and 42-54 months, respectively, which is likely to be attributed to the commencement of a second cycle of therapy.</p> <p>Costs are the highest at initial diagnosis of the disease. Treatment in the first year represents the majority of treatment costs.</p>
Relevance to economic evaluation	<p>The cost study provides estimates of treatment by risk category at the time of PCa diagnosis and by treatment pathway.</p> <p>The costs reported by treatment pathway are of most use for this economic evaluation, as resource use associated with the clinical management of patients are categorised into: AS, EBRT/brachytherapy, ADT, and radical prostatectomy alone.</p> <p>Of note, the costs for patients in "active surveillance" include patients with high risk (n=30), very high risk (n=2) and metastatic PCa (n=2). This may be reflective of the population that will undergo mpMRI should the technology become available.</p>

AIHW = Australian Institute of Health and Welfare, AR-DRG = Australian Refined Diagnostic Related Groups, CPI = consumer price index, EBRT = external beam radiotherapy, MBS = Medicare Benefits Schedule, PBS = Pharmaceutical Benefits Scheme, PSA = prostate specific antigen, PCa = prostate cancer, AS = active surveillance.

Source: Manuscript Appendix 2, Cronin et al 2016.

Prostate cancer health care costs by treatment pathway at six months and 9.5 years following diagnosis are presented in Table 58. The initial phase of treatment, which is the first six months after diagnosis, was associated with the highest cost of care for all treatment groups. After this period there was a declining trend for ongoing costs. The costs for "active surveillance/watchful waiting" were used as costs for patients undergoing AS for intermediate or low risk prostate cancer. A 50/50 average of the costs for ADT and radical prostatectomy (\$11,641 in year 1, \$2,313 in later years) was used for patients undergoing active treatment/follow up for intermediate or high risk PCa.

Table 58 Prostate cancer health care costs (initial treatment group) reported in Cronin et al (2016)

	Initial phase [6 months], mean (95% CI) ^a	Total survival adjusted [9.5 years], mean (95% CI) ^a	Year 1 ^d	Later years ^d
Active surveillance/ watchful waiting	\$4,667 (\$4,219, \$5,115)	\$8,454 (\$6,787; \$10,122)	\$5,367.47	\$981.54
EBRT/brachytherapy	\$4,064 (\$3,562, \$4,566)	\$9,621 (\$7,029; \$12,212)	\$4,805.12	\$1,117.03
ADT	\$4,850 (\$6,930, \$5,771)	\$19,210 (\$13,713; \$24,706)	\$6,183.10	\$2,230.35
Radical prostatectomy alone	\$15,217 (\$14,900, \$15,536)	\$20,636 ^c (\$19,334; \$21,938)	\$17,098.69	\$2,395.91
Systemic treatment ^b	\$19,614 (\$9,990, \$29,241)	\$55,370 (\$31,096; \$79,645)	\$23,709.62	\$6,428.65

^a: Bootstrapped 95% CI.

^b: Defined as the commencement of chemotherapy (identified in PBS or AR-DRG) or metastatic hospital admission (identified by secondary metastases ICD-10 diagnosis).

^c: reported in the publication as: \$10,636, corrected by author as \$20,636.

^d: Costs are inflated to 2014 using health CPI.

ADT = androgen deprivation therapy, CI = confidence interval, CPI = consumer price index, EBRT = external beam radiotherapy.

Source: Cronin et al (2016) Figure 1 and p7 of manuscript, accepted for publication.

Cost of delayed diagnosis

Patients with a false negative PCa diagnosis were assumed to incur additional costs to correct the diagnosis. These costs were assumed to consist of one additional PSA test and one TRUSGB, totalling \$696. For false positive patients, additional costs were assumed to be one year of AS, totalling \$982.

Costs in the economic model

A summary of all costs included in the economic model are presented in Table 59. Gordon et al. (2016) used clinical guidelines, hospital costing reports, and national Medicare reports to estimate costs for patients with a PCa diagnosis. This assessment differs from Gordon et al. (2016) as the costs for each PCa health state were obtained from the study by Cronin et al. (2016), who used linked patient data to estimate PCa costs. Both Gordon et al. (2016) and Cronin et al. (2016) report cumulative PCa costs over 10 years. In the first year, costs for low risk and intermediate risk PCa patient are similar, Gordon et al. (2016) reports higher estimated costs in the first year for high risk PCa patients (~\$17k versus ~\$9.7k). Over 10 years, similar costs are reported by both Gordon et al. (2016) and Cronin et al. (2016) in the low risk, intermediate risk and high risk PCa groups.

Table 59 Costs in economic model

Cost description	Cost (\$)	Source/calculation
Intervention costs		
Intervention: mpMRI	\$510.00	Protocol 1397 (Section A) includes cost of contrast 85% fee.
Comparator	\$604.05	Weighted average 75% TRUSGB + 25% TPUSGB.
TRUSGB	\$502.87	Griffith et al. (2016); Cost to MBS: calculation by addition of 85% fee MBS and DPMQ PBS items: \$511.75. MBS item 37219 [biopsy]: \$238.75 MBS item 55600 [ultrasound]: \$92.75 MBS item 72825 [pathology]: \$153.25 PBS item 1209P [ciprofloxacin]: \$18.12
TPUSGB	\$907.60	Griffith et al. (2016); Cost to MBS: calculation by addition of 85% fee MBS. MBS item 37219 [biopsy]: \$238.75 MBS item 55600 [ultrasound]: \$92.75 MBS item 72825 [pathology]: \$153.25 MBS item 17615 [15-30 mins]: \$72.75 MBS item 23051 [1.01hr – 1.05hr]: \$84.15 Admission theatre cost, NEP: \$265.95
MR-US fusion	\$1,021.77	Provided by CA 1424 Assessment group
MR-in gantry	\$2,346	Provided by CA 1424 Assessment group
Costs of PCa treatment		
Active surveillance 1 year After year 1	\$5,367.47 \$981.54	Cronin et al. (2016), costs inflated to 2014 using health CPI (Table 58).
Treatment of intermediate to high risk PCa 1 year After year 1	\$11,640.89 \$2,313.13	Cronin et al. 2016, costs inflated to 2014 using health CPI (Table 58). Weighted average assumes 50% radical prostatectomy, 50% ADT.
Treatment of advanced PCa 1 year After year 1	\$23,709.62 \$6,428.65	Cronin et al. (2016), costs inflated to 2014 using health CPI (Table 58).
Delayed diagnosis	\$696.01	Cost of TRUSGB/TPUSGB and PSA test.
Cost of false positive	AS	Assumption, cost of AS after the first year.
AE due to mpMRI	\$0	Assumption, no AEs.
AE due to TRUSGB	\$54.32	NHCDC 2013-14, Round 18 AR-DRG T61B, total average cost (\$4,527) x rate of sepsis (1.2%) [\$4,527*0.012]
PSA test	\$31.75	MBS item 66659/66660: 85%: \$31.75

ADT = androgen deprivation therapy, AE = adverse event, AR-DRG = Australian Refined Diagnostic Related Groups, AS = active surveillance, CPI = consumer price index, DPMQ = dispensed price for maximum quantity, MBS = Medicare Benefits Schedule, mpMRI = multiparametric MRI, NHCDC = National Hospital Cost Data Collection, PCa = prostate cancer, PSA = prostate specific antigen, TPUSGB = trans-perineal ultrasound guided biopsy, TRUSGB = trans-rectal ultrasound guided biopsy, CA = contracted assessment, NEP = National Efficient Price.

UTILITIES

Health state utility data used in the economic evaluation to estimate QALYs are discussed in Subsection C.4 and presented in Table 60.

Table 60 Utility values used in the economic model

Health state	Utility value, mean (SD) [95%CI]	Source
General Australian population of males aged 61–70y	0.82 (NR) (0.80–0.84)	Clemens et al. (2014)
low/intermediate risk PCa on AS	0.796	Stewart et al. (2005)
high/intermediate risk PCa receiving active treatment/follow-up;	0.789	Stewart et al. (2005)
advanced PCa	0.67	Stewart et al. (2005)
Disutility of biopsy (one-off)	0.035	Zhang et al. (2012)
Disutility due to AEs:		
Acute sepsis	-0.43 (assumed duration 1 month)	Stevenson et al. (2014)
Erectile dysfunction (due to PCa treatment)	-0.10 [0.05; 0.15] (assumed duration 1 year)	Cooperberg et al. (2013)
Urinary incontinence (due to PCa treatment)	-0.20 [0.1; 0.3] (assumed duration 1 year)	Cooperberg et al. (2013)
Both erectile dysfunction and urinary incontinence	-0.25 [0.125; 0.375] (assumed duration 1 year)	Cooperberg et al. (2013)

AE = adverse event, NR = not reported, PCa = prostate cancer, SD = standard deviation, CI = confidence interval, AS = active surveillance.

D.5. RESULTS OF THE ECONOMIC EVALUATION

BASE-CASE

The mpMRI can either be introduced in Population 1, or in Population 2, or in both. For each of these options, Table 61 provides the overall costs, outcomes, incremental costs and incremental outcomes for mpMRI and prostate biopsy as per the model. The table also provides the mean number of biopsies per patient in the model, for each of the strategies. A comparison of the findings from Gordon et al. (2016) and this assessment for Population 1 are also presented.

The results in Table 61 show that all strategies with mpMRI are more expensive than the strategies without mpMRI. The introduction of mpMRI in Population 1 slightly reduces the overall number of QALYs, while the introduction of mpMRI in Population 2 slightly increases the overall number of QALYs. Uncertainty around these estimates is further evaluated in section D.6. In Population 1, mpMRI is dominated (more costly, less effective) by the prostate biopsy. In Population 2, the incremental costs per QALYs gained by using mpMRI is \$12,821.

For each of the strategies, mpMRI reduces the average number of biopsies needed per patient. This reduction is largest where mpMRI is introduced for both Population 1 and 2, resulting in an average of 1.01 biopsies avoided per patient. The introduction of mpMRI results in a higher number of significant cancers diagnosed (613 versus 604 per 1,000 patients), while reducing the number of insignificant cancers diagnosed (625 versus 654 per 1,000 patients) at initial PCa diagnosis.

The incremental effectiveness estimates of the mpMRI strategies in this assessment and as reported by Gordon et al. (2016) are similar across Population 1. The incremental costs are slightly higher in this assessment compared with Gordon et al. (2016) (\$355 versus \$134). The mean numbers of biopsies avoided in Population 1 are similar. In both economic evaluations the mpMRI strategy is dominated by TRUSGB in Population 1.

Table 61 Results of the economic evaluation

		Cost	Effectiveness (QALYs)	ICER	Mean number of biopsies per patient
Population 1 only					
Intervention	mpMRI in Population 1, prostate biopsy in Population 2	\$12,990	7.40	Dominated	3.17
Comparator	Prostate biopsy in Population 1 and 2.	\$12,635	7.45		3.61
Increment		\$355	-0.05		mean 0.44 biopsies avoided per patient
Population 2 only					
Intervention	Prostate biopsy in Population 1, mpMRI in Population 2.	\$13,148	7.49	\$12,821	3.01
Comparator	Prostate biopsy in Population 1 and 2.	\$12,635	7.45		3.61
Increment		\$513	0.04		0.60 biopsies avoided per patient
Both populations					
Intervention	mpMRI in Population 1 and 2.	\$13,490	7.43	Dominated	2.60
Comparator	Prostate biopsy in Population 1 and 2.	\$12,635	7.45		3.61
Increment		\$855	-0.02		1.01 biopsies avoided per patient
Gordon et al. (2016): Population 1					
Intervention	Strategy 2: mpMRI ± MRIGB	\$24,943	7.7	Dominated	1.14
Comparator	Strategy 1: TRUSGB	\$24,203	7.82		1.44
Increment		\$740	-0.12		0.3 biopsies avoided per patient
Intervention	Strategy 3: mpMRI ± TRUSGB/ TPUSGB or MRIGB	\$24,337	7.77		1.10
Comparator	Strategy 1: TRUSGB	\$24,203	7.82		1.44

	Cost	Effectiveness (QALYs)	ICER	Mean number of biopsies per patient
Increment	\$134	-0.05	Dominated	0.34 biopsies avoided per patient

ICER = incremental cost-effectiveness ratio, mpMRI = multiparametric MRI, MRIGB = magnetic resonance guided biopsy, QALY = Quality adjusted life-year, TPUSGB = trans-perineal ultrasound guided biopsy, TRUSGB = trans-rectal ultrasound guided biopsy.

Source: CA 1397 base model; Table 12 p33 Gordon et al. (2016)

D.6. SENSITIVITY ANALYSES

In Population 1, mpMRI is dominated by prostate biopsy in each of the scenarios, except when looking at a time horizon of only five years (see sensitivity analysis I). With a five year time horizon, the ICER of mpMRI dominates prostate biopsy at \$80,264 per QALY for Population 1. In Population 2, the ICER is most sensitive to the use of MRIGB in addition to mpMRI in the intervention arm. In this sensitivity analysis (analysis A), MRIGB was assumed to be used for all patients with PI-RADS 4-5, consistent with the proposed clinical algorithm in the Protocol 1397. This increases the ICER from \$12,821 to \$66,320 per QALY gained with mpMRI.

Table 62 Key drivers of the economic model

	Description	Method/Value	ICER Population 1	ICER Population 2	ICER Population 1 and 2
	Base-case	NA	Dominated	\$12,821	Dominated
A	Use of MRIGB for patients with mpMRI PI-RADS 4-5	Sensitivity 0.85 (Schoots et al. 2014), specificity 0.97 (Pokorny et al. 2014), costs \$2,346 (based on the costs for MR-in gantry in CA 1424)	Dominated	\$66,320	Dominated
B	Accuracy of mpMRI in Population 1 obtained from the sub-sample of Australian studies	Sensitivity 54.3% instead of 73.4%; specificity 87.2% instead of 77.1% (see section C.2)	Dominated	\$12,821	Dominated
C	Reduced sensitivity and increased specificity of mpMRI	Population 1: sensitivity 57.0% instead of 73.4%; specificity 86.7% instead of 77.1%. Population 2: sensitivity 74.6% instead of 79.3%; specificity 59.8% instead of 55.1%. (based on 95% CIs, see section B.6)	Dominated	\$16,425	Dominated
D	Increased sensitivity and reduced specificity of mpMRI	Population 1: sensitivity 85.1% instead of 73.4%; specificity 63.5% instead of 77.1%. Population 2: sensitivity 83.3% instead of 79.3%; specificity 50.4% instead of 55.1%. (based on 95% CIs, see section B.6)	Dominated	\$13,329	Dominated
E	Immediate risk of disease progression to advanced PCa for false-negative patients with intermediate/high risk PCa.	0.097% (Gann et al. 2010, see CA 1424) instead of 0%	Dominated	\$17,241	Dominated
F	No disutility for biopsy	0 instead of -0.035	Dominated	\$17,094	Dominated
G	Higher disutility for biopsy	-0.05 instead of -0.035	Dominated	\$12,821	Dominated
H	Lower mpMRI fee	\$380.80 instead of \$510.02	Dominated	\$7,293	Dominated
I	Time horizon 5 years	5 years instead of 25 years (lifetime)	\$80,264	\$26,856	\$58,356
J	Time horizon 10 years	10 years instead of 25 years (lifetime)	Dominated	\$25,711	Dominated
K	No discounting	No discounting	Dominated	\$12,821	Dominated
L	Include half-cycle correction	Half-cycle correction activated in TreeAge	Dominated	\$13,864	Dominated

CI = confidence interval, ICER = incremental cost-effectiveness ratio, mpMRI = multiparametric MRI, MRIGB = magnetic resonance guided biopsy, NA = not available, PCa = prostate cancer, PI-RADS = prostate imaging reported and data system.

SECTION E

FINANCIAL IMPLICATIONS

E.1. JUSTIFICATION OF THE SELECTION OF SOURCES OF DATA

A combination of the market share approach (in Population 1 and 2) and the epidemiological approach (in Population 2) were used to estimate the financial implications of the introduction of mpMRI. Where possible, utilisation estimates from different data sources were compared. The sources of data used in the assessment are summarised in Table 63.

Table 63 Summary of data sources used

Parameter	Value	Source
Intervention costs		
mpMRI		
mpMRI	\$471.90	Protocol CA 1397 85% of \$600.00, minus cost of contrast <i>Sensitivity: \$342.75 based on similar MBS item 63476, (fee:\$403.20)</i>
Contrast for MRI (gadolinium-based)	\$38.10	MBS 63491, Fee: \$44.80, 85%: \$38.10
Patient co-payment	\$90.00	Assumption based on co-payment (Fee-85% benefit)
TRUSGB/TPUSGB		
TRUSGB/TPUSGB (75:25)	\$523.98	See section D.4 Table 59. \$523.95 when only including MBS items. Only MBS items numbers are included in value (i.e. costs are not included for PBS item 1209P or admission theatre costs for TRUSGB).
Patient co-payment	\$377.03	Department of Health, 2015/2016 Financial Year and MBS statistics
	\$82.72	Ultrasound: MBS statistics items: 55601, 55603, 55604, 55600: Weighted average of co-payment and no. of services.
	\$144.01	MBS 37219, Biopsy
	\$100.62	MBS 72825, Biopsy specimen analyse
	\$49.69	MBS 17615, General anaesthesia, initiation
Utilisation		
Market growth rate	0%	No growth, utilisation was assumed to be stable from Year 1-5
Rate of uptake of mpMRI	100%	Assumption
Patients having TRUSGB	20,149	MBS 37219: MBS statistics utilisation from July 2014 to June 2015
Population 1	13,276	Calculation: 20,149-6,873 (Population 2)=13,276
Population 2	6,873	AIHW 2016: reported 89,841 men diagnosed with PCa from 2006 to 2010; Victorian Prostate Cancer Registry (Weerakoon et al. 2015) reported Proportion of men undergoing AS, 15.3%. No. of men with Prostate cancer undergoing AS: 89,841x15.3%=13,746 Assume mpMRI once every 2 years: 13,746/2=6873

AIHW = Australian Institute of Health and Welfare, MBS = Medicare Benefits Schedule, mpMRI = multiparametric MRI, PBS = Pharmaceutical Benefits Scheme, AS = active surveillance, PCa = prostate cancer, TPUSGB = trans-perineal ultrasound guided biopsy, TRUSGB = trans-rectal ultrasound guided biopsy.

E.2. USE AND COSTS OF MPMRI

POPULATION 1 AND 2

Between July 2014 and June 2015, approximately 664,240 PSA tests were performed in Australia (MBS item 66655) (DoH 2016b). Of these, there are no data available to estimate the proportion of high/concerning PSA test results. Data from the Australian Cancer Registry, however, suggests that TRUSGB was performed in 2.9 per cent of the men who had a PSA test (Ranasinghe et al. 2014). Assuming that this is an appropriate measure, approximately 19,263 men with high/concerning PSA would undergo mpMRI per year.

Consistent with the Protocol 1397, another method to identify population numbers was derived using data from MBS item reports (MBS item 37219). This approach identified that between July 2014 and June 2015, there were 20,149 services claimed on the MBS for ultrasound-guided prostate biopsy (DoH 2016b). From this, there would potentially be 20,149 mpMRI services per year for men with suspected PCa.

Importantly, previous studies have reported that 0 to 19 per cent of men refused re-biopsy after previous biopsy of the prostate (Rosario et al. 2012); similarly men may also be unwilling to undertake an initial biopsy. Consequently, the estimations reported above may be an underestimation of utilisation, as men who refused a prostate biopsy may opt to undergo mpMRI screening.

POPULATION 2

Population 2 consists of men undergoing AS. Data from the Victorian Prostate Cancer Register indicates that 15.3 per cent of patients newly diagnosed with PCa have their disease managed with AS (Weerakoon et al. 2015). The AIHW reported that at the end of 2010, 89,841 men in Australia were living with PCa, diagnosed in the five year period between 2006-2010 (Cancer Australia 2016). From this, it was conservatively assumed that 15.3 per cent of these men living with PCa undergo AS and that this is constant over time ($89,841 \times 0.153 = 13,746$ men).

Under the proposed Protocol men undertaking AS would have a scheduled mpMRI scan at 12 months and then every three years thereafter. Men can also have an mpMRI scan at any time if there is concern about clinical or PSA changes. It was assumed that, on average, men on AS will have an mpMRI scan once every two years, then this would equate to 6,873 services for mpMRI per year.

In this evaluation it was assumed that the yearly number of mpMRIs in Population 1 and 2 is 20,149. Since the number of elderly men is rising and the uptake of new technologies is usually gradual, the number of mpMRIs may increase over the years. Conversely, the number of PSA tests and the number of ultrasound-guided prostate biopsies has been declining over the years (DoH 2016b). As it

is unknown what the resulting trend will be, the number of mpMRIs was assumed to be stable for year 1 to year 5.

POPULATION 1 VERSUS POPULATION 2

By subtracting the estimated number of 6,873 mpMRI services for Population 2 from the total 20,149 total mpMRI services results in 13,276 mpMRIs for Population 1. Table 64 provides the resulting utilisation and costs of mpMRI (including contrast) per population and in total, for year one to five after listing. Patient co-payments have been quantified, based on data provided by the DoH on covering the 2015-16 financial year. The MBS cost per mpMRI (including contrast) was assumed to be \$510, with an average co-payment of \$90.

Table 64 Use and costs of mpMRI

	Year 1	Year 2	Year 3	Year 4	Year 5	Total (Year 1-5)
Number of mpMRIs						
Population 1	13,276	13,276	13,276	13,276	13,276	66,380
Population 2	6,873	6,873	6,873	6,873	6,873	34,365
Total	20,149	20,149	20,149	20,149	20,149	100,745
Cost to the MBS						
Population 1	\$6,770,760	\$6,770,760	\$6,770,760	\$6,770,760	\$6,770,760	\$33,853,800
Population 2	\$3,505,230	\$3,505,230	\$3,505,230	\$3,505,230	\$3,505,230	\$17,526,150
Total	\$10,275,990	\$10,275,990	\$10,275,990	\$10,275,990	\$10,275,990	\$51,379,950
Patient co-payments						
Population 1	\$1,194,840	\$1,194,840	\$1,194,840	\$1,194,840	\$1,194,840	\$5,974,200
Population 2	\$618,570	\$618,570	\$618,570	\$618,570	\$618,570	\$3,092,850
Total	\$1,813,410	\$1,813,410	\$1,813,410	\$1,813,410	\$1,813,410	\$9,067,050
Total cost (MBS and patients)						
Population 1	\$7,965,600	\$7,965,600	\$7,965,600	\$7,965,600	\$7,965,600	\$39,828,000
Population 2	\$4,123,800	\$4,123,800	\$4,123,800	\$4,123,800	\$4,123,800	\$20,619,000
Total	\$12,089,400	\$12,089,400	\$12,089,400	\$12,089,400	\$12,089,400	\$60,447,000

MBS = Medicare Benefits Schedule, mpMRI = multiparametric MRI.

Source: Section E spread sheet

E.3. CHANGES IN USE AND COST OF OTHER MEDICAL SERVICES

Following the use of mpMRIs a proportion of men will avoid prostate biopsy, this may result in MBS savings due to the decrease use of the respective item number (37219, prostate biopsy). The proportion of Population 1 avoiding biopsy due to mpMRI was assumed to be equal to the probability of falling under the low-concern category. This population value (0.5) was multiplied by the probability of having a PI-RADS score of 1-3 within this category (0.594), (see economic model, section D). Similarly, the proportion of Population 2 avoiding biopsy due to mpMRI was assumed to be equal to the probability of falling under the low-concern category. Whereas this population value (0.5) was multiplied by the probability of having a PI-RADS score of 1- 3 within this category (0.499), (see economic model, section D). As a result, 29.7 per cent of Population 1 and 25.0 per cent of Population 2 was assumed to avoid prostate biopsy due to utilisation of mpMRI.

With a reduction in the number of prostate biopsies, the use of the following items was reduced accordingly: prostate ultrasound (MBS item 55600, 55601, 55603 and 55604), biopsy specimen analysis (MBS item 72825) and general anaesthesia (MBS items 17615).

Other potential cost offsets may be due to a reduction in the number of cases of biopsy-associated sepsis and changes in the number or type of PCa treatments). The potential effects of these changes on the MBS are more uncertain and have therefore been excluded from the current estimates.

Table 65 provides utilisation and cost offsets for prostate biopsies and cases of general anaesthesia resultant from mpMRI per population and in total, for year one to five after listing. Potential offsets in patient co-payments have also been quantified, based on data provided by the DoH on covering the 2015-16 financial year.

Table 65 Changes in use and costs of other medical services

	Year 1	Year 2	Year 3	Year 4	Year 5	Total (Year 1-5)
Proportion of mpMRI patients avoiding biopsy						
Population 1	0.297	0.297	0.297	0.297	0.297	0.297
Population 2	0.250	0.250	0.250	0.250	0.250	0.250
Number of biopsies avoided						
Population 1	3,943	3,943	3,943	3,943	3,943	19,715
Population 2	1,718	1,718	1,718	1,718	1,718	8,591
Savings due to TRUSGB/TPUSGB (biopsies) avoided						
Savings to the MBS						
Population 1	\$1,950,021	\$1,950,021	\$1,950,021	\$1,950,021	\$1,950,021	\$9,750,107
Population 2	\$849,771	\$849,771	\$849,771	\$849,771	\$849,771	\$4,248,856
Total	\$2,799,793	\$2,799,793	\$2,799,793	\$2,799,793	\$2,799,793	\$13,998,964
Savings to patients (co-payment)						
Population 1	\$1,339,694	\$1,339,694	\$1,339,694	\$1,339,694	\$1,339,694	\$6,698,468
Population 2	\$583,805	\$583,805	\$583,805	\$583,805	\$583,805	\$2,919,027
Total	\$1,923,499	\$1,923,499	\$1,923,499	\$1,923,499	\$1,923,499	\$9,617,495
Total savings (MBS and patients)						
Population 1	\$3,289,715	\$3,289,715	\$3,289,715	\$3,289,715	\$3,289,715	\$16,448,575
Population 2	\$1,433,577	\$1,433,577	\$1,433,577	\$1,433,577	\$1,433,577	\$7,167,884
Total	\$4,723,292	\$4,723,292	\$4,723,292	\$4,723,292	\$4,723,292	\$23,616,459

MBS = Medicare Benefits Schedule, mpMRI = multiparametric MRI, PBS = Pharmaceutical Benefits Scheme, TPUSGB = trans-perineal ultrasound guided biopsy, TRUSGB = trans-rectal ultrasound guided biopsy.

Source: Section E spreadsheet

E.4. FINANCIAL IMPLICATIONS FOR THE MBS

The financial implications to the MBS resulting from the proposed listing of mpMRI for PCa are summarised in Table 66. Listing mpMRI for Population 1 and 2 on the MBS would result in a reduced number of biopsies and an estimated saving of \$2.8 million. The total cost of listing mpMRI for both population is \$7.5 million per year (\$2.7 million and \$4.8 million per year for Population 1 and 2 respectively).

Table 66 Total costs to the MBS associated with mpMRI for prostate cancer.

	Year 1	Year 2	Year 3	Year 4	Year 5	Total (Year 1-5)
mpMRI						
Number of services	20,149	20,149	20,149	20,149	20,149	100,745
Cost to MBS						
Population 1	\$6,770,760	\$6,770,760	\$6,770,760	\$6,770,760	\$6,770,760	\$33,853,800
Population 2	\$3,505,230	\$3,505,230	\$3,505,230	\$3,505,230	\$3,505,230	\$17,526,150
Total	\$10,275,990	\$10,275,990	\$10,275,990	\$10,275,990	\$10,275,990	\$51,379,950
Savings due to TRUSGB/TPUSGB (biopsies) avoided						
Number of services	-5,661	-5,661	-5,661	-5,661	-5,661	-28,306
Savings to the MBS						
Population 1	-\$1,950,021	-\$1,950,021	-\$1,950,021	-\$1,950,021	-\$1,950,021	-\$9,750,107
Population 2	-\$849,771	-\$849,771	-\$849,771	-\$849,771	-\$849,771	-\$4,248,856
Total	-\$2,799,793	-\$2,799,793	-\$2,799,793	-\$2,799,793	-\$2,799,793	-\$13,998,964
Total cost to MBS of listing mpMRI						
Population 1	\$4,820,739	\$4,820,739	\$4,820,739	\$4,820,739	\$4,820,739	\$24,103,693
Population 2	\$2,655,459	\$2,655,459	\$2,655,459	\$2,655,459	\$2,655,459	\$13,277,294
Total	\$7,476,197	\$7,476,197	\$7,476,197	\$7,476,197	\$7,476,197	\$37,380,986

MBS = Medicare Benefits Schedule, mpMRI = multiparametric MRI, PBS = Pharmaceutical Benefits Scheme, TPUSGB = trans-perineal ultrasound guided biopsy, TRUSGB = trans-rectal ultrasound guided biopsy.

Source: Section E spreadsheet

E.5. IDENTIFICATION, ESTIMATION AND REDUCTION OF UNCERTAINTY

As discussed in section D.4, the assumed fee for mpMRI of the prostate (100% fee is \$600 including contrast), is higher than the current MBS fees for similar procedures (e.g. MBS item 63476 (MRI for the initial staging of rectal cancer) is \$403.20). A sensitivity analysis was performed to evaluate the impact of reducing the mpMRI fee from \$600 to \$448 (100% MBS fee is \$403.20 for mpMRI plus \$44.80 for contrast), resulting in 85% MBS fee of \$380.80). Table 67 shows the resulting impact on the MBS.

Table 67 Sensitivity analyses: Total costs to the MBS associated with mpMRI for prostate cancer

	Year 1	Year 2	Year 3	Year 4	Year 5	Total (Year 1-5)
Sensitivity analysis: Reduced MBS fee (\$403.20 for mpMRI + \$44.80 for contrast).						
mpMRI						
Number of services	20,149	20,149	20,149	20,149	20,149	100,745
Cost to the MBS						
Population 1	\$5,055,501	\$5,055,501	\$5,055,501	\$5,055,501	\$5,055,501	\$25,277,504
Population 2	\$2,617,238	\$2,617,238	\$2,617,238	\$2,617,238	\$2,617,238	\$13,086,192
Total	\$7,672,739	\$7,672,739	\$7,672,739	\$7,672,739	\$7,672,739	\$38,363,696
Prostate biopsies avoided						
Number of services	-5,661	-5,661	-5,661	-5,661	-5,661	-28,306
Savings to the MBS						
Population 1	-\$1,950,021	-\$1,950,021	-\$1,950,021	-\$1,950,021	-\$1,950,021	-\$9,750,107
Population 2	-\$849,771	-\$849,771	-\$849,771	-\$849,771	-\$849,771	-\$4,248,856
Total	-\$2,799,793	-\$2,799,793	-\$2,799,793	-\$2,799,793	-\$2,799,793	-\$13,998,964
Total cost to MBS of listing mpMRI						
Population 1	\$3,105,479	\$3,105,479	\$3,105,479	\$3,105,479	\$3,105,479	\$15,527,397
Population 2	\$1,767,467	\$1,767,467	\$1,767,467	\$1,767,467	\$1,767,467	\$8,837,336
Total	\$4,872,946	\$4,872,946	\$4,872,946	\$4,872,946	\$4,872,946	\$24,364,732

MBS = Medicare Benefits Schedule, mpMRI = multiparametric MRI, PBS = Pharmaceutical Benefits Scheme.

Source: Section E spread sheet

Appendix A Clinical Experts and Assessment Group

ASSESSMENT GROUP

Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S)

<u>Name</u>	<u>Position</u>
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Noted conflicts of interest

There were no conflicts of interest.

CLINICAL EXPERT

During the course of the assessment clinical input was obtained from a local expert in the field urology.

APPENDIX B

SEARCH STRATEGIES

BIBLIOGRAPHIC DATABASES

Table 68 Electronic databases searched

Electronic database	Time period searched
Embase	Inception to 20th May 2016
PubMed	Inception to 20th May 2016
The Cochrane Library (CDSR, Central, DARE, HTA, HEED)	Inception to 25th May 2016
York Centre for Reviews and Dissemination	Inception to 25th May 2016

ADDITIONAL SOURCES OF LITERATURE (INCLUDING WEBSITES)

Table 69 Website searched for this assessment

Source	Location
Australian New Zealand Clinical Trials Registry	http://www.anzctr.org.au/Default.aspx
ClinicalTrials.gov	https://clinicaltrials.gov/
Royal Australasian College of Radiologists	http://www.ranzcr.edu.au/
American College of Radiology	http://www.acr.org/
Radiological Society of North America	http://www.rsna.org/
Australian Institute of Health and Welfare	http://aihw.gov.au/
Medicare Benefits Schedule	http://www.mbsonline.gov.au
Cancer Council Victoria	http://www.cancervic.org.au/
National Guideline Clearinghouse	http://www.ahrq.gov/
Cancer Council Australia	http://www.cancer.org.au/
Australian Clinical Practice Guidelines Portal	https://www.clinicalguidelines.gov.au/
National Institute for Health and Care Excellence	https://www.nice.org.uk/
Scottish Intercollegiate Guidelines Network	http://www.sign.ac.uk/
EuroScan International Network	https://www.euroscan.org/
Trip database	https://www.tripdatabase.com/
American College of Radiology	https://www.acr.org
SA Prostate Cancer Clinical Outcomes Collaborative	https://www.sa-pccoc.com
Prostate Cancer Registry	http://pcr.registry.org.au/Home.aspx

APPENDIX C

STUDIES INCLUDED IN THE SYSTEMATIC REVIEW

PROFILES OF STUDIES FOR PATIENTS IN POPULATION 1 INCLUDED IN THE LITERATURE REVIEW

Table 70 Studies reporting diagnostic accuracy data on the use of mpMRI in Population 1

Study ID	Used in meta-analysis	Study type Enrolment ^a Design ^b	Level of evidence ^c	Location Setting	Study population characteristics: n Age years PSA ng/ml Prior biopsy	Description of Intervention: T Coil Contrast	Description of Intervention: mpMRI Reader experience	Description of Reference standard: Biopsy type	Relevant outcomes assessed	Measurement of outcomes: PI-RADS cutoff ^d
Baldisserotto et al. (2016) - key study	Yes	Case series Consecutive Retrospective	III-2	Brazil Tertiary hospital	n: 54 Age: mean 65.9 (range 53-81) PSA: mean 8.4 (SD 6.5) Prior biopsy: NR	3.0T Coil: PPAC Contrast: NR	2 urologists: with 1 or 10 years' experience	TRUSGB + cog-MRI	TP, TN, FP, FN	≥4
Baur et al. (2016) - key study	Yes	Case series Consecutive Prospective	III-2	Germany Tertiary hospital	n:45 Age: Mean 66 (range 46-81) PSA: mean 12.3 (range 5.2-70) Prior biopsy: 100%	3.0T Coil: PPAC Contrast: gadobutrol	2 readers with 3 or 5 years' experience in prostate imaging	US/MRI FGB	TP, TN, FP, FN	≥4
Dikaios et al. (2015) - key study	Yes	Case series NR Retrospective	III-2	UK Tertiary hospital	n: 85 Age: 63 (range 45-77) PSA: mean 8.66 (range 0.2-39) Prior biopsy: NR	1.5T Coil: PPAC Contrast: gadolinium- based	2 radiologists with 5 or 7 years mpMRI experience. Dedicated training of readers was undertaken	TRUSGB	TP, TN, FP, FN	≥ 4

Study ID	Used in meta-analysis	Study type Enrolment ^a Design ^b	Level of evidence ^c	Location Setting	Study population characteristics: n Age years PSA ng/ml Prior biopsy	Description of Intervention: T Coil Contrast	Description of Intervention: mpMRI Reader experience	Description of Reference standard: Biopsy type	Relevant outcomes assessed	Measurement of outcomes: PI-RADS cutoff ^d
Jambor et al. (2014) - key study	Yes	Case series NR Retrospective	III-2	Finland Tertiary hospital	n: 55 Age: median 66 (range 47-76) PSA: median 7.4 (range 4-14) Prior biopsy: 0%	3.0T Coil: body coil Contrast: Dotaren or Gadovist	NR	TRUSGB + cog-MRI	TP, TN, FP, FN	≥ 4
Lista et al. 2015 - key study	Yes	Case series NR Prospective	III-2	Spain Tertiary hospital	n: 150 Age: mean 66.2 (SD 5) PSA mean 11.3 (SD 9.6) Prior biopsy: 100%	1.5T Coil: PPAC+ERC Contrast: NR	NR	TRUSGB	TP, TN, FP, FN	≥ 4
Pokorny et al. (2014) - key study	Yes	Case series Consecutive Prospective	II	Australia Non-tertiary Hospital	n: 226 Age: Median 63 (IQR 57-68) PSA: median 5.3 (IQR 4.1-6.6) Prior biopsy: NR	3.0T Coil: NR – no ERC Contrast: NR	3 radiologists with: 1 year, 1 year or 19 years' experience. Dedicated training of readers	TRUSGB	TP, TN, FP, FN	≥ 4
Thompson et al. (2014) - key study	Yes	Case series Consecutive Prospective	III-2	Australia Secondary clinic	n: 150 Age: Median 62.4 (IQR 55-66.4) PSA: median 5.6 (IQR 4.5-7.5) Prior biopsy: NR	1.5T or 3.0T Coil: NR – no ERC Contrast: gadolinium diethylenetriami nepentaacetice acid	2 radiologists each with >1000 prior prostate mpMRIs	TRUSGB + cog-MRI	TP, TN, FP, FN	≥ 4

Study ID	Used in meta-analysis	Study type Enrolment ^a Design ^b	Level of evidence ^c	Location Setting	Study population characteristics: n Age years PSA ng/ml Prior biopsy	Description of Intervention: T Coil Contrast	Description of Intervention: mpMRI Reader experience	Description of Reference standard: Biopsy type	Relevant outcomes assessed	Measurement of outcomes: PI-RADS cutoff ^d
Thompson et al. 2016 - key study	Yes	Case series NR Prospective	III-2	Australia Secondary clinic	n: 344 Age: Median 62.9 (IQR 55.9-67.1) PSA: median 5.2 (IQR 3.7-7.1) Prior biopsy: NR	1.5T or 3.0T Coil: NR – no ERC Contrast: gadolinium diethylenetriaminepentaacetate acid	2 radiologists each with >1000 prior prostate mpMRIs	TRUSGB + cog-MRI or TRUS/MRI FGB	TP, TN, FP, FN	≥ 4
Wang et al. (2015) - key study	Yes	Case series Consecutive NR	III-2	China Tertiary hospital	n: 586 Age: mean 70.0 (SD 8.3) PSA: NR Prior biopsy: NR	1.5T Coil: PPAC + ERC Contrast: Gadopentetic dimeglumine	2 radiologists with 10 or 3 years' experience	TRUSGB	TP, TN, FP, FN	≥ 4
Zhao et al. (2016) - key study	Yes	Case series NR Retrospective	III-2	China Tertiary hospital	n: 372 Age: mean 68.5 (SD 9.2) PSA: mean 15.0 (SD 13.3) Prior biopsy: NR	3.0T Coil: body coil Contrast: NR	2 radiologists experienced in PI-RADS v2	TRUSGB + cog-MRI	TP, TN, FP, FN	≥ 4
Abd-Alazeez et al. 2014b - per hemisphere	No	Case series NR Prospective	III-2	UK Tertiary hospital	n: 54 Age: median 64 (range 39-75) PSA: median 10 (range 2-23) Prior biopsy: 100%	1.5T or 3.0T Coil: PPAC Contrast: gadoterate meglumine	8 radiologists with 3-8 years' experience	TRUSGB + cog-MRI	TP, TN, FP, FN	≥ 4
Busetto et al. (2013)	No	Case series Consecutive Prospective	III-2	Italy Tertiary hospital	n: 163 Age: mean 66.4 (SD 5.3) PSA: mean 6.8 (SD 1.6) Prior biopsy: NR	3.0T Coil: PPAC + ERC Contrast: gadolinium-based	NR	TRUSGB + cog-MRI	TP, TN, FP, FN	NA

Study ID	Used in meta-analysis	Study type Enrolment ^a Design ^b	Level of evidence ^c	Location Setting	Study population characteristics: n Age years PSA ng/ml Prior biopsy	Description of Intervention: T Coil Contrast	Description of Intervention: mpMRI Reader experience	Description of Reference standard: Biopsy type	Relevant outcomes assessed	Measurement of outcomes: PI-RADS cutoff ^d
De Visschere et al. (2016)	No	Case series Consecutive Retrospective	III-2	Belgium Tertiary hospital	n: 830 Age: mean 64.8 (range 40-83) PSA: median 8.34 (range 0.41-200) Prior biopsy: 35.8%	1.5T Coil: PPAC + ERC Contrast: NR	1 urologist with >10 years' experience	TRUSGB	TP, TN, FP, FN	NA
Ferda et al. (2013)	No	Case series NR Prospective	III-2	Czech Republic Tertiary hospital	n: 191 Age: (range 47-79) PSA: (range 4.2-123) Prior biopsy: NR	3.0T Coil: PPAC Contrast: gadobenate dimeglumine	NR	TRUSGB	TP, TN, FP, FN	NA
Girometti et al. (2012)	No	Case series Consecutive Prospective	III-2	Italy Tertiary hospital	n: 26 Age: median 64 (range 51-74) PSA: median 5.95 (range 2.52-9.74)	3.0T Coil: perineum loop coil Contrast: gadobenate dimeglumine	2 experienced radiologists	TRUSGB + cog-MRI	TP, TN, FP, FN	NA
Haffner et al. (2011)	No	Case series Consecutive Retrospective	III-2	France Tertiary hospital	n: 555 Age: median 64 (range 47-83)] PSA: median 6.75 (range 0.18-100) Prior biopsy: 0%	1.5T Coil: PPAC Contrast: gadolinium-based contrast	2 senior radiologists	TRUSGB + cog-MRI	TP, TN, FP, FN	≥ 3
Hauth et al. (2015)	No	Case series Consecutive NR	III-2	Germany Tertiary hospital	n: 94 Age: mean 63 (range 43-83) PSA: mean 9 (range 3-31) Prior biopsy: NR	1.5T Coil: PPAC Contrast: gadobutrol	2 radiologists with > 3 years' experience	TRUSGB + cog-MRI	TP, TN, FP, FN	≥ 3

Study ID	Used in meta-analysis	Study type Enrolment ^a Design ^b	Level of evidence ^c	Location Setting	Study population characteristics: n Age years PSA ng/ml Prior biopsy	Description of Intervention: T Coil Contrast	Description of Intervention: mpMRI Reader experience	Description of Reference standard: Biopsy type	Relevant outcomes assessed	Measurement of outcomes: PI-RADS cutoff ^d
Itatani et al. (2014)	No	Case series Consecutive Retrospective	III-2	Japan Tertiary hospital	n: 193 Age: mean 68.9 (SD 8.4) PSA: median 7.9 (range 1.2-159) Prior biopsy: NR	1.5T Coil: cardiac coil Contrast: gadopentate dimeglumine	3 radiologists with 5, 7 or 22 years' experience with prostate MRI	TRUSGB	TN, FN	NA
Komai et al. (2013)	No	Case series NR Prospective	III-2	Japan Tertiary hospital	n: 324 Age: men 64 (range 40-79) PSA: mean 6.8 (range 2.8-20) Prior biopsy: NR	1.5T Coil: body coil Contrast: gadopentate dimeglumine	Single radiologist with > 7 years' experience	TRUSGB + cog-MRI	TP, TN, FP, FN	≥ 3
Lamb et al. 2015	No	Case series Consecutive Retrospective	III-2	UK Tertiary hospital	n: 173 Age: G1 mean 65.1 (SD 8.1) G2 mean 68.0 (SD 10.8) PSA: G1 mean 17.5 (SD 33.5), G2 mean 7.8 (SD 3.2) Prior biopsy: NR	1.5T Coil: NR Contrast: NR	Consultant radiologists	TRUSGB	TP, TN, FP, FN	NA
Panebianco et al. (2015)	No	Case series Consecutive Prospective	III-2	Italy Tertiary hospital	n: 570 Age: mean 64 (range 51-82) PSA: >4 Prior biopsy: 0%	3.0T Coil: PPAC + ERC Contrast: NR	2 genitourinary radiologists with 13 or 14 years' experience	TRUSGB + cog-MRI	TP, TN, FP, FN	≥3
Pepe et al. (2014)	No	Case series NR Prospective	III-2	Italy Tertiary hospital	N: 168 Age: median 65 (range 49-75) PSA: mean 10.4 (range 3.7-45) Prior biopsy: 100%	3.0T Coil: PPAC Contrast: gadobutro	2 radiologists, experience NR	Saturation biopsy + cog-MRI	TP, TN, FP, FN	NA

Study ID	Used in meta-analysis	Study type Enrolment ^a Design ^b	Level of evidence ^c	Location Setting	Study population characteristics: n Age years PSA ng/ml Prior biopsy	Description of Intervention: T Coil Contrast	Description of Intervention: mpMRI Reader experience	Description of Reference standard: Biopsy type	Relevant outcomes assessed	Measurement of outcomes: PI-RADS cutoff ^d
Petrillo et al. 2013	No	Case series Consecutive Prospective	II	Italy Tertiary hospital	n: 136 Age: mean 66.35 (SD 8.4) PSA: mean 6.8 (SD 2.4) Prior biopsy: NR	1.5T Coil: PPAC + ERC Contrast: NR	2 radiologists with >5 years' experience in prostate MRI	TRUSGB	TP, TN, FP, FN	NA
Porpiglia et al. (2014)	No	Case series NR Prospective	III-1	Italy Tertiary hospital	n: 170 Age: median 65 (range 60-70) PSA: median 6.9 (IQR 5.2-9.8) Prior biopsy: 100%	1.5T Coil: PPAC + ERC Contrast: NR	Single radiologist with experience in prostate MRI	TRUSGB	TP, TN, FP, FN	NA
Renard-Penna et al. 2016	No	Case series NR Retrospective	III-2	France Tertiary hospital	n: 78 Age: median 61.72 (range 50-75) PSA: median 7.15 (range 2.5-19.7) Prior biopsy: 31%	1.5T Coil: PPAC Contrast: gadoterate meglumine	Single radiologists with >10 years' experience in prostate MRI	TRUSGB	TN, FN	≥ 3
Rosenkrantz et al. (2013)	No	Case series Consecutive Retrospective	III-2	USA Tertiary hospital	n: 42 Age: mean 63 (SD 9) PSA: mean 8.1 (SD 6.6) Prior biopsy: 69%	3.0T Coil: PPAC Contrast: NR	2 Fellowship trained radiologists	TRUSGB + cog-MRI	TP, TN, FP, FN	NA
Rouse et al. (2011)	No	Case series Consecutive Prospective	III-2	UK Tertiary hospital	n: 114 Age: mean 63.6 (SD 9) PSA: median 8.0 (range 0-228) Prior biopsy: 100%	1.5T Coil: NR Contrast: gadolinium-based contrast	Single urologist with >10 years' experience	TRUSGB + cog-MRI	TP, TN, FP, FN	≥ 3
Tamada et al. (2011)	No	Case series Consecutive Retrospective	III-2	Japan Tertiary hospital	N: 50 Age: mean 70 (range 40-84) PSA: median 6.68 (range 4.1-9.9) Prior biopsy: NR	1.5T Coil: PPAC Contrast: gadopentate dimeglumine	Two radiologists with 11 and 7 years' experience	TRUSGB	TP, TN, FP, FN	NA

Study ID	Used in meta-analysis	Study type Enrolment ^a Design ^b	Level of evidence ^c	Location Setting	Study population characteristics: n Age years PSA ng/ml Prior biopsy	Description of Intervention: T Coil Contrast	Description of Intervention: mpMRI Reader experience	Description of Reference standard: Biopsy type	Relevant outcomes assessed	Measurement of outcomes: PI-RADS cutoff ^d
Tanimoto et al. (2007)	No	Case series Consecutive Prospective	III-2	Japan Tertiary hospital	n: 83 Age: mean 67.4 (range 53-87) PSA: mean 19.4 (range 4.3-33.2) Prior biopsy: NR	1.5T Coil: torso coil Contrast: gadopentate dimeglumine	Two readers. Experience NR	TRUSGB	TP, TN, FP, FN	NA
Tonttila et al. (2016)	No	Single arm of an RCT Consecutive Prospective	III-2	Finland Tertiary hospital	n: 113 Age: median 63 (IQR 60-66) PSA: median 6.1 (IQR 4.2-9.9) Prior biopsy: 0%	3.0T Coil: body and spine coils Contrast: NR	Two experience radiologists not experienced in mpMRI.	TRUSGB + cog-MRI	TP, TN, FP, FN	NA
Vilanova et al. (2011)	No	Case series Consecutive Retrospective	II	Spain Tertiary hospital	n: 70 Age: mean 63.5 (range 43-87) PSA: median 7.4 (range 4-17) Prior biopsy: 0%	1.5T Coil: PPAC + ERC Contrast: dimeglumine	Three radiologists with 14, 8 or 6 years' experience in prostate MRI	TRUSGB	TP, TN, FP, FN	≥ 3
Washino et al. (2016)	No	Case series NR Retrospective	III-1	Japan Tertiary hospital	n: 288 Age: mean 69 (SD 20) PSA: mean 7.5 (IQR 5.5-11.0) Prior biopsy: 0%	1.5T or 3.0T Coil: PPAC Contrast: NR	Single urologist with 14 years prostate MRI experience	TRUSGB + cog-MRI	TN, FN	≥ 3
Wysock et al. (2016)	No	Case series Consecutive Retrospective	III-2	USA Tertiary hospital	n: 54 Age: G1: median 61 (IQR 53.8-66), G2 median 64 (IQR 57.3-68.8) PSA: G1 median 3.7 (IQR 3.9-4.9), G2 median 5.3 (IQR 4.2-8.4) Prior biopsy: NR	3.0T Coil: PPAC Contrast: NR	Single fellowship trained radiologist with expertise in prostate MRI	TRUSGB	TP, TN, FP, FN	≥1

^a: Describes consecutive or non-consecutive enrolment.

^b: Describes a retrospective or prospective study design.

c: Source: [NHMRC hierarchy of evidence](#)^d: If PI-RADS ≥ 4 was used by the study or was calculable by the assessment group this is denoted. For studies that only reported data for another PI-RADS cut-off, e.g. ≥ 3 this is listed. For studies that did not use the PI-RADS system, this is denoted not applicable (NA)

NR = not reported, TP = true positive, FP = false positive, TN = true negative, FN = false negative, PPAC = pelvic phased array coil, ERC = endorectal coil, mpMRI = multiparametric- MRI, TRUSGB = trans-rectal ultrasound-guided biopsy, FGB = fusion guided biopsy, MRI = magnetic resonance imaging, IQR = interquartile range, PSA = prostate-specific antigen, cog-MRI = cognitive –guided MRI biopsy, PI-RADS = Prostate Imaging Reporting and Data System.

PROFILES OF STUDIES FOR PATIENTS IN POPULATION 2 INCLUDED IN THE SYSTEMATIC LITERATURE REVIEW

Table 71 Studies reporting diagnostic accuracy data on the use of mpMRI in Population 2

Study ID	Used in meta-analysis	Study type Enrolment ^a Design ^b	Level of evidence ^c	Location Setting	Study population characteristics: n Age years PSA ng/ml Gleason score	Description of Intervention: T Coil Contrast	Description of Intervention: mpMRI Reader experience	Description of Reference standard:	Relevant outcomes assessed	Measurement of outcomes PI-RADS cutoff ^d
Abd-Alazeez et al. (2014) - key study	Yes	Case series Prospective NR	III-2	UK Tertiary hospital	n: 137 Age: G1 mean 62.7 (SD 5.8), G2 mean 61.5 (SD 5.7), G3 mean 59.4 (SD 8.2) PSA: G1 median 7 (range 2-29), G2 median 8.3 (range 2.3-17), G3 median 5 (range 2.8-15) Gleason: 6	1.5T or 3.0T Coil: PPAC Contrast: meglumine gadoterate	5 radiologists with experience reporting at least 100 mpMRI per year	TRUSGB + cog-MRI	TP, TN, FP, FN	4
Almeida et al. (2016) - key study	Yes	Case series Prospective NR	III-2	Italy Tertiary hospital	n: 73 Age: mean 63 (SD 5.9) PSA: mean 6.03 (SD 1.93) Gleason: ≤ 6	1.5T Coil: PPAC Contrast: gadopentetate dimeglumine	2 radiologists experienced in prostate MRI	prostatectomy	TP, TN, FP, FN	4
de Cobelli et al. 2015 - key study	Yes	Case series Retrospective NR	III-2	Italy Tertiary hospital	n: 223 Age: mean 62.8 (SD 8.28) PSA: mean 6.02 (SD 1.91) Gleason: ≤ 6	1.5T Coil: ERC Contrast: gadopentetate dimeglumine	Single radiologist. Experience NR	prostatectomy	TP, TN, FP, FN	4

Study ID	Used in meta-analysis	Study type Enrolment ^a Design ^b	Level of evidence ^c	Location Setting	Study population characteristics: n Age years PSA ng/ml Gleason score	Description of Intervention: T Coil Contrast	Description of Intervention: mpMRI Reader experience	Description of Reference standard:	Relevant outcomes assessed	Measurement of outcomes PI-RADS cutoff ^d
Flavell et al. (2014) - key study	Yes	Case series Retrospective NR	III-2	USA Tertiary hospital	n: 64 Age: median 60.7 (range 45.1-74.5) PSA: median 4.7 (range 0.6-9.7) Gleason: 6	1.5T or 3.0T Coil: PPAC + ERC Contrast: NR	2 radiologists with 2 or 15 years' experience.	TRUSGB + cog-MRI	TP, TN, FP, FN	4
Porpiglia et al. (2015) - key study	Yes	Case series Retrospective NR	III-2	Italy Tertiary hospital	n: 120 Age: G1 median 65 (IQR 57-70) G2 median 66 (IQR 64-69) PSA: G1 median 7 (IQR 6.39-10.1) G2 median 5.75 (IQR 4.88-9.22) Gleason: ≤ 6	1.5T Coil: PPAC + ERC Contrast: NR	2 experienced radiologists	prostatectomy	TP, TN, FP, FN	4
Rebcal et al. (2016) - key study	Yes	Case series Retrospective Consecutive	III-2	USA Tertiary hospital	n: 206 Age: median 63 (IQR 57-68) PSA: median 5.2 (IQR 3.8-7.4) Gleason: ≤ 6	1.5T or 3.0T Coil: PPAC ± ERC Contrast: NR	6 radiologists with 6-15 years' experience	TRUSGB	TP, TN, FP, FN	4
Bonekamp et al. (2013)	No	Case series Retrospective Consecutive	III-2	USA Tertiary hospital	n: 73 Age: median 67 (IQR 62-70) PSA: median 4.5 (IQR 3.7-5.6) Gleason: ≤ 6	3.0T Coil: body coil + ERC Contrast: gadopentate dimeglumine	Single genitourinary radiologist with >10 years' experience in prostate MRI	TRUSGB	TP, TN, FP, FN	NA
Felker et al. (2016)	No	Case series Retrospective Consecutive	III-2	USA Tertiary hospital	n: 49 Age: mean 65 (range 47-80) PSA: median 5 (IQR 2.5-6.4) Gleason: 6	3.0T Coil: NR Contrast: NR	2 Fellowship trained genitourinary radiologists with >1,000 mpMRIs experience	TRUSGB + cog-MRI	TP, TN, FP, FN	NA

Study ID	Used in meta-analysis	Study type Enrolment ^a Design ^b	Level of evidence ^c	Location Setting	Study population characteristics: n Age years PSA ng/ml Gleason score	Description of Intervention: T Coil Contrast	Description of Intervention: mpMRI Reader experience	Description of Reference standard:	Relevant outcomes assessed	Measurement of outcomes PI-RADS cutoff ^d
Margel et al. (2012)	No	Case series Prospective Consecutive	III-2	Canada Tertiary hospital	n: 60 Age: G1 mean 62.6 (SD 7), G2 mean 63.5 (SD 6), G3 mean 64 (SD 8.2) PSA: G1 median 5.9 (range 1.7-10), G2 median 4.4 (range 1.1-9.1), G3 median 4.1 (range 1.1-9.9) Gleason: ≤ 6	1.5T Coil: PPAC + ERC Contrast: gadopentate-diethylenetetraminepentacetic acid	Single experienced radiologist	TRUSGB + cog-MRI	TP, TN, FP, FN	NA
Mullins et al. 2013	No	Case series Retrospective Consecutive	III-2	USA Tertiary hospital	n: 37 Age: median 67 (range 49-80) PSA: median 4.5 (range 0.4-18.6) Gleason: ≤ 6	3.0T Coil: body coil + ERC Contrast: gadopentate dimeglumine-DTPA	Single radiologists with >10 years' experience in prostate MRI	TRUSGB	TP, TN, FP, FN	NA
Sahibzada et al. 2016	No	Case series Retrospective Consecutive	III-2	UK Tertiary hospital	n: 100 Age: mean 69.8 (range 59.1-85.9) PSA: mean 6.5 (range 3.4-17.5) Gleason: ≤ 6	1.5T or 3.0T Coil: NR Contrast: NR	Single radiologists with >10 years' experience in prostate MRI	TRUSGB	TP, TN, FP, FN	NA
Siddiqui et al. 2015	No	Case series Retrospective NR	III-2	USA Tertiary hospital	n: 60 Age: mean 60.2 PSA: mean 4.8 Gleason: ≤ 6	3.0T Coil: cardiac coil + ERC Contrast: NR	NR	TRUSGB + cog-MRI	Graphical outcomes only	NA
Stamatakis et al. (2013)	No	Case series Retrospective NR	III-2	USA Tertiary hospital	n: 85 Age: mean 60.2 (range 40-79) PSA: mean 4.8 (0.2-10.9) Gleason: ≤ 6	3.0T Coil: cardiac coil + ERC Contrast: NR	NR	TRUSGB + cog-MRI	TP, TN, FP, FN	NA

Study ID	Used in meta-analysis	Study type Enrolment ^a Design ^b	Level of evidence ^c	Location Setting	Study population characteristics: n Age years PSA ng/ml Gleason score	Description of Intervention: T Coil Contrast	Description of Intervention: mpMRI Reader experience	Description of Reference standard:	Relevant outcomes assessed	Measurement of outcomes PI-RADS cutoff ^d
Vos et al. 2016	No	Case series Prospective NR	III-2	USA Tertiary hospital	n: 24 Age: median 65 (range 51-75) PSA: median 6.4 (range 1.4-14.3) Gleason: ≤ 6	3.0T Coil: built-in body coil Contrast: ProHance	NR	NR	TP, TN, FP, FN	3
Walton Diaz et al. (2015)	No	Case series Retrospective NR	III-2	USA Tertiary hospital	n: 58 Age: mean 61.4 (range 40-79) PSA: mean 5.2 (range 0.2-23.3) Gleason: ≤ 6	3.0T Coil: body coil + ERC Contrast: NR	2 experienced genitourinary radiologists with 7 or 14 years prostate MRI experience	TRUSGB + cog-MRI	TP, TN, FP, FN	NA
Wysock et al. (2016)	No	Case series Prospective Consecutive	III-2	USA Tertiary hospital	n: 73 Age: median 63 (IQR 57-68) PSA: median 5.4 (IQR 1.7-6.5) Gleason: 6	3.0T Coil: PPAC Contrast: NR	Single fellowship trained radiologist with expertise in prostate imaging	TRUSGB	TN, FN	1

^a: Describes consecutive or non-consecutive enrolment.

^b: Describes a retrospective or prospective study design.

^c: Source: [NHMRC hierarchy of evidence](#). ^d: If PI-RADS ≥4 was used by the study or was calculable by the assessment group this is denoted. For studies that only reported data for another PI-RADS cut-off, e.g. ≥ 3 this is listed. For studies that did not use the PI-RADS system, this is denoted not applicable (NA).

NR = not reported, TP = true positive, FP = false positive, TN = true negative, FN = false negative, PPAC = pelvic phased array coil, ERC = endorectal coil, mpMRI = multiparametric- MRI, TRUSGB = trans-rectal ultrasound-guided biopsy, FGB = fusion guided biopsy, MRI = magnetic resonance imaging, IQR = interquartile range, PSA = prostate specific antigen, cog-MRI = cognitive –guided MRI biopsy, PI-RADS = Prostate Imaging Reporting and Data System.

PROFILES OF STUDIES REPORTING PATIENT OUTCOMES

Table 72 Studies reporting patient outcomes due to delayed treatment of PCa

Study ID	Study type Enrolment ^a Design ^b	Level of evidence ^c	Location Setting	Study population characteristics: n Age years Risk of disease	Type of treatment	Length of delay	Relevant outcomes assessed
Van den bergh et al. (2013)	Systematic review of level III studies	Level III	NA	The review included studies with patients diagnosed with PCa. A total of 17 studies with 34,517 patients were included. Patient baseline characteristics were not reported by the review	Radical prostatectomy and/or radiation therapy	Ranged from <3months to >2 years delay	OS, CSS, BCR, MF, LNI, ECE, PSM, TU
Redaniel et al. (2013)	Cohort study Consecutive Retrospective	Level III-3	UK Review of all cases registered in national cancer registry	n: 17,043 Age: 15-54 years – 11.68%, 55-64 years – 51.86%, >65 years – 36.46% Risk: NR	Prostatectomy	Median 95 days (IQR 70-125). Study compared delay 0-3 months with 4-6 months delay	OS
Eroglu et al. (2014)	Cohort study NR Retrospective	Level III-3	Turkey Tertiary hospital	n: 290 Age: G1 mean 66.0 (SD 7.2), G2 mean 65.0 (SD 5.6) Risk: NR	Radical prostatectomy	NR	TU
Dong et al. (2016)	Cohort study NR Retrospective	Level III-3	USA Secondary clinic	n: 4,064 Age: median 68 Risk: low – 57.9%, intermediate – 29.9%, high – 12.2%	Radiation therapy	Up to 24 months delay	BCR, MF, OS
Boorjian et al. (2005)	Cohort study Consecutive Retrospective	Level III-3	USA Secondary clinic	n: 3,149 Age: median 61 (IQR 56-65) Risk: low – 70%, intermediate – 25%, high – 5%	Radical prostatectomy	Study compared <3 months to >3 months delay	BCR

Study ID	Study type Enrolment ^a Design ^b	Level of evidence ^c	Location Setting	Study population characteristics: n Age years Risk of disease	Type of treatment	Length of delay	Relevant outcomes assessed
O'Kelly et al. (2013)	Cohort study Consecutive Retrospective	Level III-3	Ireland Secondary clinic	n: 350 Age: mean 62.35 Risk: low-78.4%, intermediate or high – 21.6%	Surgery or radiation	Study compared <12 months, 12-18 months and >18 months delays	TU
Loeb et al. (2016)	Cohort study Consecutive Retrospective	Level III-3	Sweden Review of all cases registered in national cancer registry	n: 7,608 Age: median 62.0 (IQR 58.3-65.5) Risk: low – 68%, intermediate – 27%, high – 2%, NR – 3%	Radical prostatectomy	Study compared <12 months, 2-24 months and >24 months delays	CSS, ECE, PSM
Hussein et al. (2015)	Cohort study NR Retrospective	Level III-3	USA Tertiary hospital	n: 219 Age: mean 61.6 (range 42-82) Risk: NA ^d	Radical prostatectomy	Study compared median delay of 28 month (IQR 16-52 months)	PSM

^a: Describes consecutive or non-consecutive enrolment.

^b: Describes a retrospective or prospective study design.

^c: Source: [NHMRC hierarchy of evidence](#)^d This study included patients on AS who were upgraded to intermediate or high risk cancer.

IQR = interquartile range, NR = not reported, NA = not applicable, G1 = group 1, G2 = group 2, OS = overall survival, CSS = cancer specific survival, BCR = biochemical recurrence, MF = metastases formation, LNI = lymph node involvement, ECE = extracapsular extension, PSM = positive surgical margins, TU = tumour upgrade.

PROFILES OF STUDIES ON THE SAFETY OF THE TRUSGB INCLUDED IN THE SYSTEMATIC LITERATURE REVIEW

Table 73 Studies reporting safety outcomes associated with TRUSGB

Study ID	Used in meta-analysis	Study type Enrolment ^a Design ^b	Level of evidence ^c	Location Setting	Study population characteristics n Age years PSA ng/ml PSA density Prior biopsy (%)	Description of Biopsy type Cores Enema (%) Needle thickness	Relevant outcomes assessed (i.e. related to outcomes specified in PICO)
Anastasiadis et al. (2015)	No	Case series Non-consecutive Prospective	IV	UK Multiple hospitals	n: 198,361 Age: 45-54: 3.2% 55-64: 21.5% 65-74: 40.5% 75-84: 28.9% ≥85: 5.9% PSA: NR Prior biopsy: NR	TRUSGB Cores: 10-12 Enema: NR Needle: NR	UTI Urinary obstruction Haematuria Hospitalisation
Carignan et al. (2012)	No	Case-control Consecutive Retrospective	III-2	Canada Tertiary hospital	n: 5,798 Age: 66.7 [61.8-72.0] PSA: NR Prior biopsy: NR	TRUSGB Cores: 12 Enema: 28 Needle: NR	Major infection UTI Hospitalisation Bacteraemia
Nam et al. (2013)	No	Case series Non-consecutive Retrospective	IV	Canada Multiple hospitals	n: 75,190 Age: <50=3.1 51-59=21.1 70-79=41.6 ≥80=4.7 PSA: NR Prior biopsy: 0	TRUSGB Cores: NR Enema: NR Needle: NR	Minor infection Urinary obstruction Hospitalisation bleeding

Study ID	Used in meta-analysis	Study type Enrolment ^a Design ^b	Level of evidence ^c	Location Setting	Study population characteristics n Age years PSA ng/ml PSA density Prior biopsy (%)	Description of Biopsy type Cores Enema (%) Needle thickness	Relevant outcomes assessed (i.e. related to outcomes specified in PICO)
Roth et al. (2015)	No	Case series Non-consecutive Retrospective	IV	Australia Multiple hospitals	n: 34,865 Age: mean 64 PSA: NR Prior biopsy: mix	TRUSGB Cores: NR Enema: NR Needle: NR	Minor infection Major infection UTI Urinary obstruction Haematuria Hospitalisation Prostatitis Fever
Pinsky et al. (2014)	No	Cohort study Consecutive Prospective	III-2	USA Multiple hospitals	n: 4,836 Age: 65.5 (5.3) PSA: NR Prior biopsy: mix	Route: NR Guidance: NR Cores: NR Enema: NR Needle: NR	Minor infection Urinary obstruction Rectal bleeding Death
Roberts et al. (2002)	No	Case series Non-consecutive retrospective	IV	USA Multiple hospitals	n: 1,776 Age: <60=23% 60-69=36% 70-79=32% >80=9% PSA: ≤4.0=1% 4.1-10.0=30% ≥10.1=20% unknown=49% Prior biopsy: mix	Route: mix Guidance: NR Cores: 1-5=46% 6=17% ≥7=19% unknown=18% Enema: 0 Needle: 18G	Minor infection UTI Urinary obstruction Haematuria Rectal bleeding Blood in ejaculate Pain Bacteraemia Hospitalisation

Study ID	Used in meta-analysis	Study type Enrolment ^a Design ^b	Level of evidence ^c	Location Setting	Study population characteristics n Age years PSA ng/ml PSA density Prior biopsy (%)	Description of Biopsy type Cores Enema (%) Needle thickness	Relevant outcomes assessed (i.e. related to outcomes specified in PICO)
Rosario et al. (2012)	No	Comparative study with concurrent controls Non-consecutive Prospective	III-2	UK Multiple hospitals	n: 1,147 Age: 62.1 (5.1) PSA: 4.2 (3.5-5.8) Prior biopsy: 0	TRUSGB Cores: NR Enema: NR Needle: NR	Haematuria Rectal bleeding Haemospermia Pain Fever
Simsir et al. (2010)	No	Case series Consecutive Retrospective	IV	Turkey Tertiary hospital	n: 2,023 Age: 64.3 (10.1) PSA: 26.7 Prior biopsy: mix	TRUSGB Cores: 12 [10-20] Enema: 100 Needle: NR	Major infection Death
Zaytoun et al. (2011)	No	Case series Non-consecutive Retrospective	IV	USA Tertiary hospital	n: 1,348 Age: 64.4 (8.7) PSA: 8.0 (4.0-8.1) Prior biopsy: NR	TRUSGB Cores: 12 [10-20] Enema: 35 Needle: NR	Minor infection Major infection Urinary obstruction Haematuria Rectal bleeding Haemospermia
Helfand et al. (2012)	No	Case series Non-consecutive Prospective	IV	USA Tertiary hospital	n: 85 Age: 61.0 (8.3) PSA: 52 (3.4) Prior biopsy: 0	TRUSGB Cores: 12 Enema: NR Needle: NR	Erectile dysfunction
Kariotis et al. (2010)	No	Comparative study with concurrent controls Non-consecutive Prospective	III-2	Greece Tertiary hospital	n: 434 Age: 65.4 PSA: 7.4 Prior biopsy: 0	TRUSGB Cores: 12 + targeted Enema: NR Needle: 18G	Haematuria Rectal bleeding Haemospermia

Study ID	Used in meta-analysis	Study type Enrolment ^a Design ^b	Level of evidence ^c	Location Setting	Study population characteristics n Age years PSA ng/ml PSA density Prior biopsy (%)	Description of Biopsy type Cores Enema (%) Needle thickness	Relevant outcomes assessed (i.e. related to outcomes specified in PICO)
Marino et al. (2015)	No	Cohort study with concurrent controls Non-consecutive Retrospective	III-2	USA Tertiary hospital	n: 455 Age: median 65 PSA: NR Prior biopsy: NR	TRUSGB Cores: NR Enema: NR Needle: NR	Major infection UTI
Mohammed et al. (2016)	No	Comparative study with historical controls Consecutive Retrospective	III-3	Ireland Tertiary hospital	n: 286 Age: Group A: 59.6 (6.6) Group B: 61 (6.2) PSA: Group A: 9 (5.1) Group B: 8.5 (4.6) Prior biopsy: mix	TRUSGB Cores: 6/12 Enema: 100 Needle: NR	Bacteraemia Hospitalisation
Petteffi et al. (2002)	No	RCT Consecutive Prospective	II	Brazil Multiple hospitals	n: 105 Age: Group A: 65 (7) Group B: 64 (8) PSA: NR Prior biopsy: NR	TRUSGB Cores: NR Enema: 100 Needle: 18G	UTI Fever Hospitalisation
Sahin et al. (2015)	No	Comparative study with concurrent controls Non-consecutive Prospective	III-2	Turkey Tertiary hospital	n: 480 Age: 65.9 (7.8) PSA: 12.5 (18.8) Prior biopsy: 28	TRUSGB Cores: 12 Enema: 100 Needle: 18G	Minor infection Major infection UTI

Study ID	Used in meta-analysis	Study type Enrolment ^a Design ^b	Level of evidence ^c	Location Setting	Study population characteristics n Age years PSA ng/ml PSA density Prior biopsy (%)	Description of Biopsy type Cores Enema (%) Needle thickness	Relevant outcomes assessed (i.e. related to outcomes specified in PICO)
Solberg et al. (2011)	No	RCT Consecutive Prospective	II	Norway, Sweden Multiple hospitals	n: 875 Age: 66.1 (5.9) PSA: 16 (8-27) Prior biopsy: 100	TRUSGB Cores: NR Enema: 0 Needle: NR	Urinary obstruction Pain
Utrera et al. (2011a)	No	Case series Non-consecutive Prospective	IV	Spain Tertiary hospital	n: 220 Age: 69.5 (7.9) PSA: 12.7 (28.7) Prior biopsy: mix	TRUSGB Cores: 13.5 (1.7) Enema: 100 Needle: NR	Urinary obstruction Bacteraemia Bacteriuria Fever Hospitalisation
Utrera et al. (2011b)	No	Case series Non-consecutive Retrospective	IV	Spain Tertiary hospital	n: 144 Age: 66 (6.4) PSA: 14.4 (12.6) Prior biopsy: 100	TRUSGB Cores: 30.4 (3.8) Enema: 100 Needle: NR	Major infection Urinary obstruction Haematuria Prostatitis Rectal bleeding
Loeb et al. (2013)	No	Systematic review NR NR	IV	USA Multiple hospitals	n: 11 studies, 2,705 patients Age: NR PSA: NR Prior biopsy: NR	TRUSGB Cores: NR Enema: NR Needle: NR	Haematuria Haemospermia Rectal bleeding Erectile dysfunction

^a: Describes consecutive or non-consecutive enrolment.

^b: Describes a retrospective or prospective study design.

^c: Source: [NHMRC hierarchy of evidence](#) NR = not reported, PSA = prostate specific antigen, TRUSGB = trans-rectal ultrasound guided biopsy, RCT = randomised controlled trial, UTI = urinary tract infection, PICO = participant intervention comparator outcome.

PROFILES OF STUDIES ON THE SAFETY OF THE TPUSGB INCLUDED IN THE SYSTEMATIC LITERATURE REVIEW

Table 74 Studies reporting safety outcomes associated with TPUSGB

Study ID	Used in meta-analysis	Study type Enrolment ^a Design ^b	Level of evidence ^c	Location Setting	Study population characteristics n Age years PSA ng/ml PSA density Prior biopsy (%)	Description of Biopsy type	Relevant outcomes assessed (i.e. related to outcomes specified in PICO)
Mai et al. (2016)	No	Case series Non-consecutive NR	IV	China Tertiary hospital	n: 3,007 Age: 70 [30-91] PSA: 11.0 (0.2-100) Prior biopsy: 0	Guidance: US Cores: NR Enema: NR Needle: 18G	Infection Urinary obstruction Haematuria Hospitalisation Mild haematuria Haemospermia Perineal haematoma Rectal bleeding
Chang et al. (2013)	No	Narrative review NR NR	IV	Australia, Multiple hospitals	n: 34 studies, 8,044 patients Age: NR PSA: Mean 1.2-23.6 Prior biopsy: Mixed	Guidance: US Cores: NR Enema: NR Needle: NR	Infection Urinary obstruction Haematuria Hospitalisation UTI Fever

^a: Describes consecutive or non-consecutive enrolment.

^b: Describes a retrospective or prospective study design.

^c: Source: [NHMRC hierarchy of evidence](#) NR = not reported, PSA = prostate specific antigen, US = ultrasound, UTI = urinary tract infection, PICO = participant intervention comparator outcome.

APPENDIX D

EVIDENCE PROFILE TABLES

POPULATION 1: MEN WITH SUSPICION OF PROSTATE CANCER

Table 75 Evidence profile table for the accuracy of mpMRI compared to biopsy for men with suspected prostate cancer (assumed prevalence 35% in men with low-concern and 50% in men with high-concern). mpMRI has a sensitivity of 73%, 95%CI [57, 85]; and a specificity of 77%, 95%CI [64, 87]

Outcome ^a	Patients/Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of patients per 100 tested for mpMRI (low concern)	Number of patients per 100 tested for mpMRI (high concern)	Test accuracy QoE	Importance
True positives	2,062 patients (10 studies).	not serious	serious ¹	not serious	serious ²	none	257 (199 to 298)	367 (285 to 426)	⊕⊕⊕⊖ LOW	Critical
False positives	2,062 patients (10 studies).	not serious	serious ¹	not serious	serious ²	none	149 (86 to 237)	114 (66 to 182)	⊕⊕⊕⊖ LOW	Critical
True negatives	2,062 patients (10 studies).	not serious	serious ¹	not serious	serious ²	none	501 (413 to 564)	386 (318 to 434)	⊕⊕⊕⊖ LOW	Critical
False negatives	2,062 patients (10 studies).	not serious	serious ¹	not serious	serious ²	none	93 (52 to 151)	133 (74 to 215)	⊕⊕⊕⊖ LOW	Critical

^a: GRADE Working Group grades of evidence (Guyatt et al. 2013).

⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.

⊕⊕⊕⊖ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

⊕⊕⊖⊖ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

⊕⊖⊖⊖ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

¹: No explanation for the observed heterogeneity could be found. ² The wide confidence interval reflects imprecision.

QoE = quality of evidence, CI = confidence interval.

Table 76 Evidence profile table for the impact of delayed treatment due to a false negative on mpMRI compared to biopsy for Population 1

Outcome ^a	Patients/Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Result	Impact of change in management QoE	Importance
Overall survival	41,146 patients (5 studies).	not serious	not serious	serious ¹	not serious	none	Delay did not impact overall survival (results from 5 studies)	⊕⊙⊙⊙ VERY LOW	Critical
Cancer free survival	8,916 patients (2 studies).	not serious	not serious	serious ¹	not serious	none	Delay did not impact cancer free survival (results from 2 studies)	⊕⊙⊙⊙ VERY LOW	Critical
Rate of metastases formation	6,681 patients (4 studies).	not serious	not serious	serious ¹	not serious	none	Delay did not impact rate of metastases formation (results from 4 studies)	⊕⊙⊙⊙ VERY LOW	Critical
Biochemical recurrence	19,768 patients (14 studies).	not serious	not serious	serious ¹	not serious	none	3 studies reported recurrence was associated with delayed treatment, 11 studies reported no impact.	⊕⊙⊙⊙ VERY LOW	Critical
Extra-capsular extension	16,039 patients (7 studies).	not serious	not serious	serious ¹	not serious	none	Delay did not impact rate of extra-capsular extension (results from 7 studies)	⊕⊙⊙⊙ VERY LOW	Important
Lymph node involvement	3,605 patients (3 studies).	not serious	not serious	serious ¹	not serious	none	Delay did not impact rates of lymph node involvement (results from 3 studies)	⊕⊙⊙⊙ VERY LOW	Important

Positive surgical margins	14,413 patients (6 studies).	not serious	not serious	serious ¹	not serious	none	One study reported a delay >9 months was associated with an increase in the rate of positive surgical margins in patients with intermediate risk disease. 8 studies reported no impact from delayed treatment	⊕⊖⊖⊖ VERY LOW	Important
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^a: GRADE Working Group grades of evidence (Guyatt et al. 2013)

⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.

⊕⊕⊕⊖ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

⊕⊕⊖⊖ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

⊕⊖⊖⊖ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

¹: Indirectness was rated serious: this was due to the delay in the included studies being shorter than what would likely be experienced by patients in our population.

²: Noting the small number of included studies; however both studies had >300 patients.

³: Noting the small number of included studies; however median sample size was >300 patients.

QoE = quality of evidence.

POPULATION 2: MEN ON ACTIVE SURVEILLANCE

Table 77 Evidence profile table for the accuracy of mpMRI compared to biopsy for detected upgrade cancer in men on active surveillance (assumed prevalence 30%) mpMRI (sensitivity 79%, 95%CI [75, 83]; specificity 55%, 95%CI [50, 60])

Outcome ^a	Patients/Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of patients per 100 tested for mpMRI (low risk men)	Test accuracy QoE	Importance
True positives	820 patients (6 studies).	not serious	not serious	not serious	not serious ¹	none	238 (224 to 250)	⊕⊕⊕⊕ HIGH	Critical
False positives	820 patients (6 studies).	not serious	not serious	not serious	not serious ¹	none	314 (281 to 347)	⊕⊕⊕⊕ HIGH	Critical
True negatives	820 patients (6 studies).	not serious	not serious	not serious	not serious ¹	none	386 (353 to 419)	⊕⊕⊕⊕ HIGH	Critical
False negatives	820 patients (6 studies).	not serious	not serious	not serious	not serious ¹	none	62 (50 to 76)	⊕⊕⊕⊕ HIGH	Critical

^a: GRADE Working Group grades of evidence (Guyatt et al. 2013)

⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.

⊕⊕⊕⊙ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

⊕⊕⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

¹: While the confidence intervals indicated a high level of precision, the relatively moderate number of studies and the moderate median population size may warrant downgrade.

QoE = quality of evidence.

Table 78 Evidence profile table for the impact of delayed treatment due to a false negative on mpMRI compared to biopsy for Population 2

Outcome ^a	Patients/Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Result	Impact of change in management QoE	Importance
Positive surgical margins	219 patients (1 study).	not serious	not serious	not serious	serious ¹	none	Results from a single study found no difference in the rate of positive surgical margins associated with a delay to treatment following tumour upgrade	⊕⊖⊖⊖ VERY LOW	Important

^a GRADE Working Group grades of evidence (Guyatt et al. 2013)

⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.

⊕⊕⊕⊖ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

⊕⊕⊖⊖ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.




⊕⊖⊖⊖ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.



¹. Only a single study was used to inform this outcome.

QoE = quality of evidence.


HARMS ASSOCIATED WITH BIOPSY


Table 79 Evidence profile table for the adverse events associated with biopsy

Outcome ^a	Patients/Studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Result	QoE	Importance
Major Infection	45,492 patients (8 studies).	not serious	not serious	not serious	not serious	none	Major infection ranged from 0.2 per cent to 2.4 per cent in the trans-rectal biopsy studies. There was no major infection reported in the trans-perineal biopsy studies.	 LOW	Critical
Minor infection	132,239 patients (9 studies).	not serious	not serious	not serious	not serious	none	Minor infection ranged from 0.0 per cent to 0.03 per cent in the trans-perineal biopsy studies and from 0.7 per cent to 6.9 per cent in the trans-rectal biopsy studies.	 LOW	Critical
Re-hospitalisation	292,956 patients (9 studies).	not serious	not serious	not serious	not serious	none	Re-hospitalisation ranged from 0.7 per cent to 2.1 per cent in the trans-perineal biopsy studies and from 0.4 per cent to 5.5 per cent in the trans-rectal biopsy studies.	 LOW	Critical

Bleeding related outcomes	334,688 patients (13 studies).	not serious	serious ¹	serious ²	not serious	none	Bleeding ranged from 0.1 per cent to 6.1 per cent in the trans-perineal biopsy studies and from 0.8 per cent to 88.0 per cent in the trans-rectal biopsy studies.	 VERY LOW	Important
Urinary obstruction	132,020 patients (12 studies).	not serious	serious ¹	not serious	not serious	none	Urinary obstruction ranged from 0.4 per cent to 38.0 per cent in the trans-perineal biopsy studies and from 0.8 per cent to 21.0 per cent in the trans-rectal biopsy studies.	 VERY LOW	Important

^a: GRADE Working Group grades of evidence (Guyatt et al. 2013)

 **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.

 **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

 **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

 **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

¹: Based on self-reported data.

²: One study only included men on blood-thinning medication.

CI = confidence interval, QoE = quality of evidence.

STUDIES EXCLUDED FROM THE DIAGNOSTIC ACCURACY OF BIOPSY SEARCH

Excluded due to full-text unavailable

Ciatto, S, Bonardi, R, Lombardi, C, Cappelli, G, Castagnoli, A, D'Agata, A, Zappa, M & Gervasi, G 2001, 'Predicting prostate biopsy outcome by findings at digital rectal examination, transrectal ultrasonography, psa, psa density and free-to-total psa ratio in a population-based screening setting', *International Journal of Biological Markers*, vol.16(3), pp. 179-82.

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STUDIES EXCLUDED FROM THE DIAGNOSTIC ACCURACY SEARCH

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STUDIES EXCLUDED FROM THE SAFETY SEARCH

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TRIGGERING QUESTIONS FOR THE QUADAS-2 TOOL

Table 80 QUADAS triggering questions

Question	Criteria for Y/N/unclear	Notes
Was patient enrolment consecutive or random?	<p>YES: Study should state consecutive patients or that assignment to each arm was randomised.</p> <p>NO: Study states not consecutive or not random assignment (or describe assignment that is not random).</p> <p>UNCLEAR: If not described how patients were enrolled or assigned to a group then mark as unclear.</p>	Studies should enrol consecutive patients or randomly allocate. If not there is potential for bias.
Was case-control design avoided?	<p>YES: Case control design avoided.</p> <p>NO: Case control design used.</p> <p>Unclear: Study does not report whether patients are known or suspected of having disease and whether a group of healthy patients were also included.</p>	Case control design is when a group of people known to have disease and a control group of people without the disease are enrolled. This may exaggerate diagnostic accuracy because borderline cases are excluded.
Did the study avoid inappropriate exclusions?	<p>YES: All patients were excluded appropriately (i.e. all had suspicion of disease, no other inappropriate exclusions).</p> <p>NO: Study made inappropriate exclusions.</p> <p>Unclear: study does not report any exclusion criteria.</p>	<p>Inappropriate exclusions are for example only including patients known to have the disease. Our studies should all include patients suspected of PCa but not confirmed (for pop 1) or those undergoing surveillance without any indication of whether their disease has progressed or not.</p> <p>Only including confirmed cases exaggerates sensitivity because borderline cases or cases where diagnosis is difficult or those that may be FN have been excluded.</p>
Applicability	What aspects of study patients do not match the protocol?	This is where, for example, we are interested in all patients with suspected PCa but paper only includes those at low risk, or those at very high risk.
Were index test results interpreted without knowledge of the reference standard?	<p>YES: Study states that MRI images were read without knowledge of biopsy results OR MRI images were read before biopsy performed.</p> <p>NO: Study states MRI readers had knowledge of biopsy results.</p> <p>Unclear: Study does not mention any blinding.</p>	This refers to blinding – knowledge of the biopsy results may influence reading of the MRI.
Was the threshold for a positive result pre-specified i.e. PI-RADS \geq 4	<p>YES: Methods section states PI-RADS threshold used to determine a positive from a negative.</p> <p>NO: Study states PI-RADS ratio was determined after imaging or more than one threshold was trialled to optimise diagnostic accuracy.</p> <p>Unclear: Study does not report whether PI-RADS was determined before or after study</p>	Selecting the PI-RADS criteria during the study to optimise results may overestimate diagnostic accuracy – results are likely to be worse in an independent sample of patients for whom the ratio has not been optimised.

Question	Criteria for Y/N/unclear	Notes
	started.	
Applicability	What aspects of intervention do not match the review question?	This may include things like the threshold in the protocol for a yes is PI-RADS 4 or 5, the study may use ≥ 3 .
Is the reference standard likely to correctly classify the condition?	YES: An appropriate reference standard (biopsy or follow-up or surgical specimen) used. NO: An inappropriate reference standard used i.e. CT, or PET – NOT these studies should have been excluded. Unclear: Study doesn't report reference standard NOTE – these should be excluded.	Diagnostic accuracy assumes reference standard is 100% sensitive and 100% specific and is therefore accurately able to assess the performance of other diagnostic tests.
Were reference standard results interpreted without knowledge of the index test?	YES: Study states e.g. biopsy results read without knowledge of MRI (blind). NO: Study states e.g. biopsy results read with knowledge of MRI. Unclear: study doesn't mention this standard.	As above, knowing the e.g. MRI results could influence the biopsy results and therefore introduce bias.
Applicability	Are there concerns the reference standard might be different from the specifications in the protocol.	
Was the reference standard performed within 90 days of the index test?	YES: Study reports timing of e.g. both MRI and biopsy and these are within 30 days. NO: Study reports timing of e.g. MRI and biopsy but these are not within 90 days. Unclear: Study does not report timing of tests.	Ideally results of e.g. MRI and biopsy would be performed on the same day but not always applicable.
Did all patients receive a reference standard	YES: all received a reference standard (biopsy or follow-up or surgical specimen) NO: not all received a reference standard Unclear: study does not report whether all received a reference standard.	All patients must receive a valid reference standard – this is an inclusion criteria for our CA.
Did all patients receive the same reference standard?	YES: All patients received e.g. biopsy. NO: Some patients received biopsy, some were followed up and some had surgery (or any other combination). Unclear: Study does not report this info – unlikely.	This assess verification bias, for example if those with high risk by MRI get biopsy but low risk on MRI do not receive biopsy and are followed up then some false negatives may be inaccurately classified as true negatives by clinical follow-up.
Were all patients included in the analysis	YES: Number in effectiveness outcomes (TP, TN, FP, FN) match the number included in the study after exclusion criteria applied. NO: Some patients lost to follow-up. Unclear: Study doesn't report how many were included (possible?) or doesn't report how many in results (unlikely). Unclear: It also may be unclear if the included number reported is before or after losses to follow-up.	All recruited patients should be in analysis. Bias may be introduced by losses to follow-up.

PCa = prostate cancer, MRI = Magnetic resonance imaging, PI-RADS = Prostate Imaging Reporting and Data System, CT = computed tomography, PET = positron emission tomography, CA = contracted assessment, TP = true positive, FP = false positive, TN = true negative, FN = false negative

REFERENCE STANDARD (SECTION B3.1)

Table 81 Risk of bias assessment for systematic reviews reporting the diagnostic accuracy of biopsy (AMSTAR)

Review characteristics	Shen et al. (2012)	Schoots et al. (2015)
Was an 'a priori' design provided?	😊	😊
Was there duplicate study selection and data extraction?	😊	😊
Was a comprehensive literature search performed?	😊	😊
Was the status of publication (i.e. grey literature) used as an inclusion criterion?	😊	😊
Was a list of studies (included and excluded) provided?	😞	😞
Were the characteristics of the included studies provided?	😊	😊
Was the scientific quality of the included studies assessed and documented?	😊	😊
Was the scientific quality of the included studies used appropriately in formulating conclusions?	😊	😊
Were the methods used to combine the findings of studies appropriate?	😊	😊
Was the likelihood of publication bias assessed?	😊	😊
Was the conflict of interest stated?	😊	😊

😊 = low risk, 😞 = high risk, ? = unclear risk.

DIAGNOSTIC ACCURACY STUDIES POPULATION 1 (SECTION B3.3)

Table 82 Quality appraisal of studies assessing the diagnostic accuracy of mpMRI in Population 1 using the QUADAS-2 tool

Study	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Abd-Alazeez et al. 2014b	?	😊	?	?	😊	😊	😊
Baldisserotto et al. (2016)	😊	😞	😊	?	😊	😊	😊
Baur et al. (2016)	😊	😊	😞	😞	😊	😊	😊
Busetto et al. (2013)	😊	?	😞	?	😊	😞	😊
De Visschere et al. (2016)	😊	😊	?	?	😊	😞	😊
Dikaios et al. (2015)	?	?	?	😞	😊	😊	😊
Ferda et al. (2013)	😞	😊	?	😞	😊	😞	😊

Study	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Girometti et al. (2012)	😊	😊	😞	😞	😊	😞	😊
Haffner et al. (2011)	😊	😊	😞	😊	😊	😞	😊
Hauth et al. (2015)	😊	?	?	😊	😊	😞	😊
Itatani et al. (2014)	😊	😊	?	😞	😞	😞	😊
Jambor et al. (2014)	?	?	?	?	?	😊	😊
Komai et al. (2013)	?	😊	😞	😊	😊	😞	😊
Lamb et al. 2015	😊	?	?	?	😊	😞	😊
Lista et al. 2015	?	😊	😊	?	😊	😊	😊
Panebianco et al. (2015)	😊	?	?	?	😊	😞	😊
Pepe et al. (2014)	?	😊	😞	😊	?	😞	😊
Petrillo et al. 2013	😊	😊	😊	?	😊	😞	😊
Pokorny et al. (2014)	😊	😊	😊	😞	😊	😊	😊
Porpiglia et al. (2014)	?	😊	😊	?	😊	😞	😊
Renard-Penna et al. 2016	😊	😊	?	?	😞	😞	😊
Rosenkrantz et al. (2013)	😊	😊	😞	😊	😊	😞	😊
Rouse et al. (2011)	😊	😊	😞	?	😊	😞	😊
Tamada et al. (2011)	😊	😊	?	😊	😊	😞	😊
Tanimoto et al. (2007)	?	?	?	😞	😊	😞	😊
Thompson et al. (2014)	😊	😊	😞	?	😊	😊	😊
Thompson et al. 2016	?	😊	?	?	😊	😊	😊
Tonttila et al. (2016)	😊	😊	😞	?	😊	😞	😊
Vilanova et al. (2011)	😊	😊	😊	😞	😊	😞	😊
Wang et al. (2015)	😊	😊	😞	😞	😊	😊	😊

Risk of bias					Applicability concerns		
Study	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Washino et al. (2016)	?	😊	😞	😞	😞	😞	😊
Wysock et al. (2016)	?	?	?	?	😞	😞	😊
Zhao et al. (2016)	?	?	😞	😊	😊	😊	😊

😊 = low risk, 😞 = high risk, ? = unclear risk.

CLINICAL UTILITY STUDIES (SECTION B5.2.3)

Table 83 Quality appraisal of systematic reviews using AMSTAR

Review characteristics	van den Bergh et al. (2013)
Was an 'a priori' design provided?	😊
Was there duplicate study selection and data extraction?	?
Was a comprehensive literature search performed?	😊
Was the status of publication (i.e. grey literature) used as an inclusion criterion?	😞
Was a list of studies (included and excluded) provided?	😞
Were the characteristics of the included studies provided?	😊
Was the scientific quality of the included studies assessed and documented?	😞
Was the scientific quality of the included studies used appropriately in formulating conclusions?	😞
Were the methods used to combine the findings of studies appropriate?	NA
Was the likelihood of publication bias assessed?	😞
Was the conflict of interest stated?	😞

😊 = criteria met, 😞 = criteria not met, ? = not clear from reporting if criteria met, NA = not applicable.

Table 84 Quality appraisal of non-comparative studies using modified Downs and Black checklist for non-randomized studies

Study ID	Boorjian et al. (2005)	Dong et al. (2016)	Eroglu et al. (2014)	Hussein et al. (2015)	Loeb et al. (2016)	O'Kelly et al. (2013)	Redaniel et al. (2013)
Is the hypothesis/aim/objective of the study clearly described?	😊	😊	😊	😊	😊	😊	😊
Are the main outcomes to be measured clearly described in the Introduction or Methods section?	😊	😊	😊	😊	😊	😊	😊
Are the characteristics of the patients included in the study clearly described?	😊	😊	😊	😊	😊	😊	😊

Study ID	Boorjian et al. (2005)	Dong et al. (2016)	Eroglu et al. (2014)	Hussein et al. (2015)	Loeb et al. (2016)	O'Kelly et al. (2013)	Redaniel et al. (2013)
Are the interventions of interest clearly described?	NA	NA	NA	NA	NA	NA	NA
Are the distributions of principal confounders in each group of subjects to be compared clearly described?	😊	😊	😊	😊	😊	😊	😊
Are the main findings of the study clearly described?	😊	😊	😊	😊	😊	😊	😊
Does the study provide estimates of the random variability in the data for the main outcomes?	😊	😊	😊	😊	😊	😊	😊
Have all important adverse events that may be a consequence of the intervention been reported?	NA	NA	NA	NA	NA	NA	NA
Have the characteristics of patients lost to follow-up been described?	NA	NA	NA	NA	NA	NA	NA
Have actual probability values been reported for the main outcomes except where the probability value is less than 0.001?	😊	😊	😊	😊	😊	😊	😞
Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	😊	😊	😊	😊	😊	😊	😊
Were those subjects who were prepared to participate, representative of the entire population from which they were recruited?	😊	😊	😊	😊	😊	😊	😊
Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	😊	😊	😊	😊	😊	😊	😊
Was an attempt made to blind study subjects to the intervention they have received?	😞	😞	😞	😞	😞	😞	😞
Was an attempt made to blind those measuring the main outcomes of the intervention?	😞	😞	😞	😞	😞	😞	😞
If any of the results of the study were based on "data dredging", was this made clear?	😊	😊	😊	😊	😊	😊	😊

Study ID	Boorjian et al. (2005)	Dong et al. (2016)	Eroglu et al. (2014)	Hussein et al. (2015)	Loeb et al. (2016)	O'Kelly et al. (2013)	Redaniel et al. (2013)
In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case control studies, is the time period between the intervention and outcome the same for cases and controls?	😊	😊	😊	😊	😊	😊	😊
Were the statistical tests used to assess the main outcomes appropriate?	😊	😊	😊	😊	😊	😊	😊
Was compliance with the intervention/s reliable?	😊	😊	😊	😊	😊	😊	😊
Were the main outcome measures used accurate (valid and reliable)?	😊	😊	😊	😊	😊	😊	😊
Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	?	?	😊	😊	?	?	?
Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same time?	😊	😊	😊	😊	😊	😊	😊
Were study subjects randomised to intervention groups?	😞	😞	😞	😞	😞	😞	😞
Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	NA	NA	NA	NA	NA	NA	NA
Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	?	?	😊	😊	?	?	😊
Were losses of patients to follow-up taken into account?	😞	😞	😞	😞	😞	😞	😞
Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance <5%?	😊	😊	😊	😊	😊	😊	😊

😊 = Yes, 😞 = No, NA = not applicable, ? = cannot answer.

DIAGNOSTIC ACCURACY STUDIES POPULATION 2 (SECTION B6.3)

Table 85 QUADAS-2 results: Population 2

Study	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Abd-Alazeez et al. (2014)	?	😊	😞	😞	😊	😊	😊
Almeida et al. (2016)	?	😊	?	😞	😊	😊	?
Bonekamp et al. (2013)	?	😊	?	😞	😊	😞	😊
de Cobelli et al. 2015	?	😊	?	?	😊	😊	?
Felker et al. (2016)	😊	😊	😞	?	😊	😞	😊
Flavell et al. (2014)	?	😞	😞	?	😊	😊	😊
Margel et al. (2012)	😊	?	😞	😞	😊	😞	😊
Mullins et al. 2013	😊	😞	?	😞	😊	😞	😊
Porpiglia et al. (2015)	?	😊	😊	😊	😊	😊	?
Rebcal et al. (2016)	😊	😊	😞	?	😊	😊	😊
Sahibzada et al. 2016	😊	?	😊	?	😊	😞	😊
Siddiqui et al. 2015	?	😊	?	?	😊	😞	😊
Stamatakis et al. (2013)	?	😞	😞	?	😊	😞	😊
Vos et al. 2016	?	😊	?	😞	😊	😞	😊
Walton Diaz et al. (2015)	?	?	😞	?	😊	😞	😊
Wysock et al. (2016)	?	?	?	?	😊	😊	😊

😊 = low risk, 😞 = high risk, ? = unclear risk.

RISK OF HARM (SECTION B7)

Table 86 Quality appraisal of the systematic reviews using the AMSTAR tool

Review characteristics	Chang et al. (2013)	Loeb et al. (2013)
Was an 'a priori' design provided?	☹	☺
Was there duplicate study selection and data extraction?	☹	?
Was a comprehensive literature search performed?	☹	☺
Was the status of publication (i.e. grey literature) used as an inclusion criterion?	☹	☹
Was a list of studies (included and excluded) provided?	☹	☹
Were the characteristics of the included studies provided?	☺	☺
Was the scientific quality of the included studies assessed and documented?	☹	☹
Was the scientific quality of the included studies used appropriately in formulating conclusions?	☺	☹
Were the methods used to combine the findings of studies appropriate?	☺	☺
Was the likelihood of publication bias assessed?	☹	☹
Was the conflict of interest stated?	☺	☺
Score (/11)	4	5

☺ = Yes, ☹ = No, ? = cannot answer.

Table 87 Quality appraisal of the Randomised Controlled Trial using Cochrane Collaboration's tool for assessing risk of bias in randomised trials (Petteffi et al. (2002))

Bias	Authors' judgment
Random sequence generation (selection bias)	U
Allocation concealment (selection bias)	L
Blinding of patients and researchers (performance bias)	U
Blinding of outcome assessment (detection bias)	U
Incomplete outcome data (attrition bias)	L
Selective reporting (reporting bias)	L
Other bias	L

U = unclear, L = low risk of bias, H = high risk of bias.

Table 88 Quality appraisal of the comparative studies using modified Downs and Black checklist for non-randomized studies

Author	Mohammed et al. (2016)	Marino et al. (2015)	Sahin et al. (2015)	Pinsky et al. (2014)	Carignan et al. (2012)	Rosario et al. (2012)	Zaytoun et al. (2011)	Kariotis et al. (2010)
Is the hypothesis/aim/objective of the study clearly described?	☺	☺	☺	☺	☺	☺	☺	☺
Are the main outcomes to be measured clearly described in the Introduction or Methods section?	☺	☺	☺	☺	☺	☺	☺	☺
Are the characteristics of the patients included in the study clearly described?	☺	☺	☺	☺	☺	☹	☹	☺
Are the interventions of interest clearly described?	☺	☺	☺	☺	☹	☹	☺	☺
Are the distributions of principal confounders in each group of subjects to be compared clearly described?	☺	☹	☺	☺	☺	☺	☺	☺
Are the main findings of the study clearly described?	☺	☺	☺	☺	☺	☺	☺	☺
Does the study provide estimates of the random variability in the data for the main outcomes?	☺	☹	☺	☺	☺	☺	☺	☺
Have all important adverse events that may be a consequence of the intervention been reported?	☺	☺	☺	☺	☹	☺	☺	☹
Have the characteristics of patients lost to follow-up been described?	☹	☹	☹	☹	☹	☺	☹	☺
Have actual probability values	☺	☺	☺	☺	☺	☹	☺	☺

Author	Mohammed et al. (2016)	Marino et al. (2015)	Sahin et al. (2015)	Pinsky et al. (2014)	Carignan et al. (2012)	Rosario et al. (2012)	Zaytoun et al. (2011)	Kariotis et al. (2010)
been reported for the main outcomes except where the probability value is less than 0.001?								
Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	😊	😊	😊	😊	😊	😊	😊	😞
Were those subjects who were prepared to participate, representative of the entire population from which they were recruited?	NA	NA	NA	NA	NA	NA	NA	NA
Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	😞	😊	😞	😊	😊	😊	😞	😞
Was an attempt made to blind study subjects to the intervention they have received?	NA	NA	NA	NA	NA	NA	NA	NA
Was an attempt made to blind those measuring the main outcomes of the intervention?	NA	NA	NA	NA	NA	NA	NA	NA
If any of the results of the study were based on “data dredging”, was this made clear?	😞	😞	😞	😞	😞	😞	😞	😞
In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case control studies, is the time period between the	😞	😊	😞	😊	😊	😊	😊	😊

Author	Mohammed et al. (2016)	Marino et al. (2015)	Sahin et al. (2015)	Pinsky et al. (2014)	Carignan et al. (2012)	Rosario et al. (2012)	Zaytoun et al. (2011)	Kariotis et al. (2010)
intervention and outcome the same for cases and controls?								
Were the statistical tests used to assess the main outcomes appropriate?	😊	😊	😊	😊	😊	😊	😊	😊
Was compliance with the intervention/s reliable?	😊	😊	😊	😊	😊	😊	😊	😊
Were the main outcome measures used accurate (valid and reliable)?	😊	😊	😊	😊	😊	😞	😊	😞
Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	?	?	?	?	?	?	?	?
Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same time?	😞	😊	😊	😊	😊	😊	😊	😊
Were study subjects randomised to intervention groups?	😞	😊	😞	😞	😞	😞	😞	😞
Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	😞	😞	😞	😞	😞	😞	😞	😞

Author	Mohammed et al. (2016)	Marino et al. (2015)	Sahin et al. (2015)	Pinsky et al. (2014)	Carignan et al. (2012)	Rosario et al. (2012)	Zaytoun et al. (2011)	Kariotis et al. (2010)
Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	☺	☺	☺	NA	NA	☺	☺	☹
Were losses of patients to follow-up taken into account?	☹	☺	☺	☺	☺	☺	☹	☺
Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance <5%?	☹	☹	☹	☺	☺	☺	☹	☺
Total /27	14	17	16	19	16	17	16	14

☺ = Yes, ☹ = No, NA = not applicable, ? = cannot answer.

Table 89 Quality appraisal of the case series studies using Downs and Black tool

Study ID	Mai et al. (2016)	Anastasiadis et al. (2015)	Roth et al. (2015)	Nam et al. (2013)	Helfand et al. (2012)	Solberg et al. (2011)	Utrera et al. (2011a)	Utrera et al. (2011b)	Simsir et al. (2010)	Roberts et al. (2002)
STUDY OBJECTIVE										
1. Is the hypothesis/aim/objective of the study clearly stated in the abstract, introduction, or methods section?	1	1	1	1	1	1	1	1	1	1
STUDY POPULATION										
2. Are the characteristics of the patients included in the study described?	1	0	0	1	1	1	1	1	1	1
3. Were the cases collected in more than one centre?	0	1	1	1	0	1	0	?	0	1
4. Are the eligibility criteria (inclusion and exclusion criteria) to enter the study explicit and appropriate?	1	1	1	1	1	1	1	0	0	1
5. Were patients recruited consecutively?	0	0	0	0	0	1	0	0	0	0
6. Did patients enter the study at a similar point in the disease?	1	1	1	1	1	0	1	1	1	1
INTERVENTION AND CO-INTERVENTION										
7. Was the intervention clearly described in the study?	1	1	1	0	1	1	1	1	1	1
8. Were additional interventions clearly reported in the study?	1	1	1	1	1	1	1	1	1	1
OUTCOME MEASURES										
9. Are the outcome measures clearly defined in the introduction or methods section?	0	1	1	1	1	1	1	1	1	1

10. Were relevant outcomes appropriately measured with objective and/or subjective methods?	1	1	1	1	0	0	0	?	1	1
11. Were outcomes measured before and after intervention?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
14. Was the loss to follow-up reported?	0	0	1	0	0	NA	0	0	0	0
15. Does the study provide estimates of random variability in the data analysis of relevant outcomes?	1	0	0	0	1	NA	0	1	1	0
16. Are adverse events reported?	1	1	1	1	1	1	1	1	1	1
17. Are the conclusions of the study supported by the results?	1	1	1	1	1	1	1	1	1	1
COMPETING INTEREST AND SOURCE OF SUPPORT										
18. Are both competing interest and source of support for the study reported?	1	1	1	1	1	1	0	0	0	1
TOTAL /18	11	11	12	11	11	11	9	9	10	12

1 = yes, 0 = no.

APPENDIX G DIAGNOSTIC ACCURACY RESULTS

FROM STUDIES WITH APPLICABILITY ISSUES

POPULATION 1 STUDIES USING A PI-RAS \geq 3 THRESHOLD

Table 90 Summary of findings for the accuracy of mpMRI, relative to biopsy, in patients with conditions with assumed pre-test probability (prevalence) of 35%

Outcomes	mpMRI – all cancer [95%CI]	mpMRI – clinically significant cancer [95%CI]	Quality of evidence	Importance
Sensitivity	87.5% [76.8, 93.6]	96.5% [61.8, 99.8]	⊕⊕⊖⊖ Low ^{1,2}	Not important
Specificity	57.7% [28.8, 82.1]	69.8% [45.2, 84.6]	⊕⊕⊖⊖ Low ^{1,2}	Not important

^a: GRADE Working Group grades of evidence (Guyatt et al. 2013).

⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.

⊕⊕⊕⊖ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

⊕⊕⊖⊖ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

⊕⊖⊖⊖ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

1: No explanation for the observed heterogeneity could be found.

2: The wide confidence interval reflects imprecision.

Figure 18 HSROC curve for studies using a PI-RADS ≥ 3 threshold for the detection of any cancer

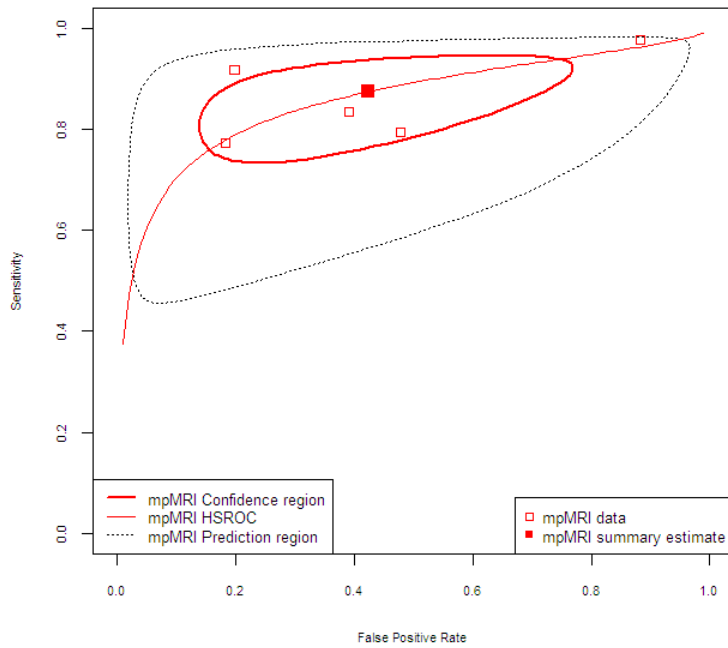
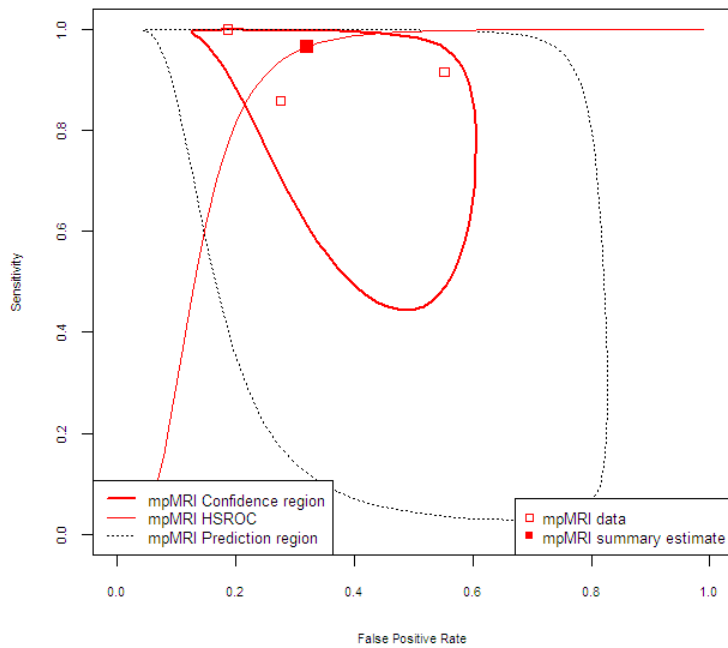


Figure 19 HSROC curve for studies using a PI-RADS ≥ 3 threshold for the detection of clinically significant cancer



POPULATION 1 PI-RADS NOT USED OR THRESHOLD NOT REPORTED

Table 91 Summary of findings for the accuracy of mpMRI, relative to biopsy, in patients with conditions with assumed pre-test probability (prevalence) of 35%

Outcomes	mpMRI – all cancer [95%CI]	mpMRI – clinically significant cancer [95%CI]	Quality of evidence	Importance
Sensitivity	85.1% [79.3, 89.5]	84.9% [80.9, 88.2]	⊕⊕⊕⊖ Low ^{1,2}	Not important
Specificity	65.9% [55.1, 75.2]	55.4% [43.1, 66.7]	⊕⊕⊕⊖ Low ^{1,2}	Not important

^a: GRADE Working Group grades of evidence (Guyatt et al., 2013).

⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.

⊕⊕⊕⊖ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

⊕⊕⊖⊖ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

⊕⊖⊖⊖ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

1: No explanation for the observed heterogeneity could be found.

2: The wide confidence interval reflects imprecision.

Figure 20 HSROC curve for studies not reporting the threshold or not using PI-RADS for the detection of any cancer

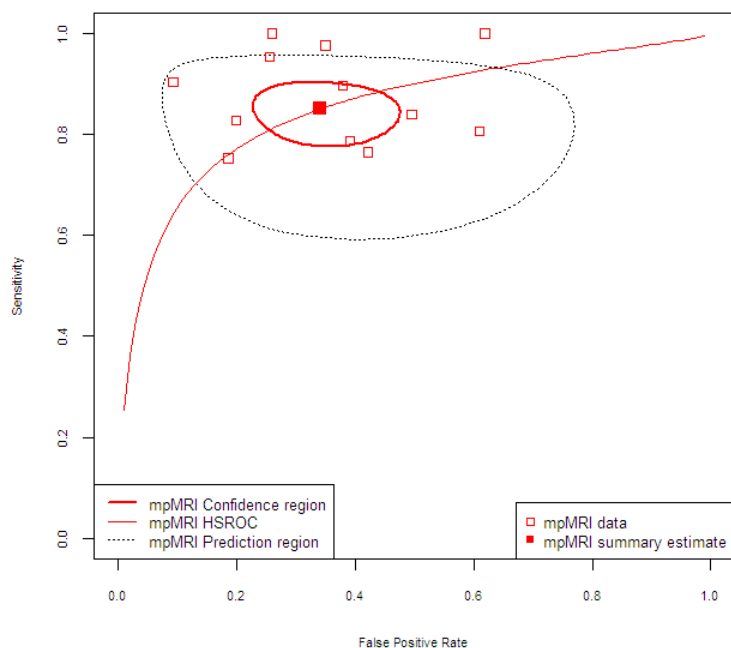
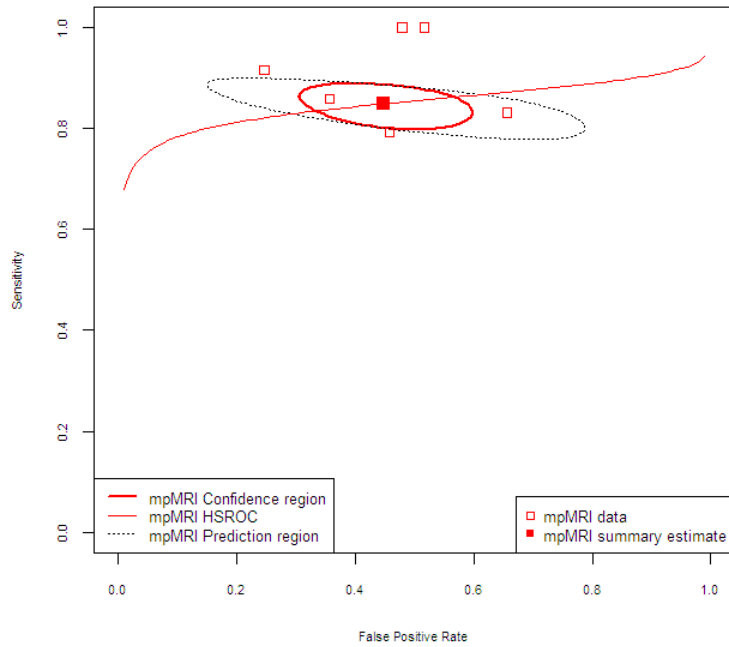


Figure 21 HSROC curve for studies not reporting the threshold or not using PI-RADS for the detection of clinically significant cancer



POPULATION 2 STUDIES USING A PI-RADS ≥ 3 THRESHOLD

Note: only a single study reported use of a PI-RADS ≥ 3 threshold for a positive result therefore no meta-analysis was undertaken

POPULATION 2 PI-RADS NOT USED OR THRESHOLD NOT REPORTED

Table 92 Summary of findings for the accuracy of mpMRI, relative to biopsy for detecting cancer upgrade in patients on active surveillance with an assumed pre-test probability (prevalence) of 30%

Outcomes	mpMRI – all cancer [95%CI]	Quality of evidence	Importance
Sensitivity	62.2% [42.2, 78.7]	⊕⊕⊖⊖ Low ^{1,2}	Not important
Specificity	69.9% [32.4, 91.9]	⊕⊕⊖⊖ Low ^{1,2}	Not important

^a: GRADE Working Group grades of evidence (Guyatt et al. 2013).

⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.

⊕⊕⊕⊖ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

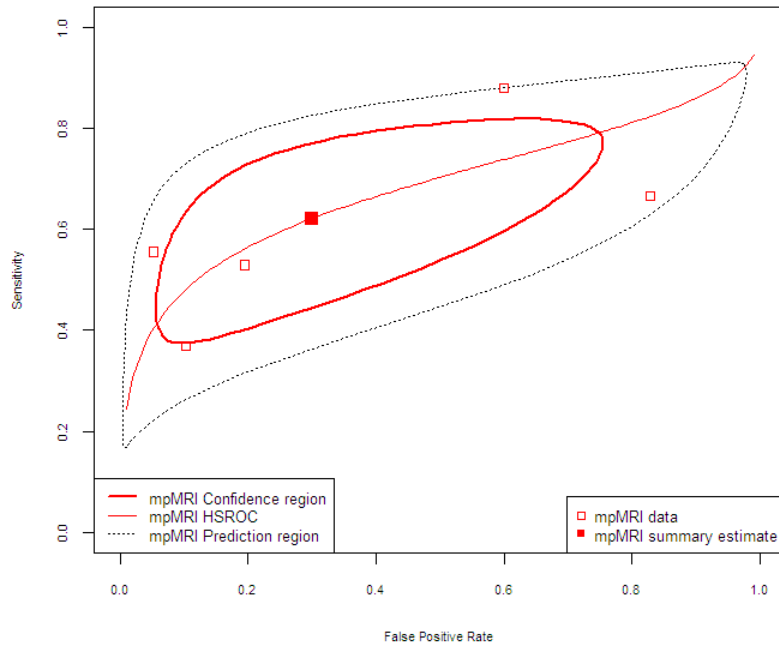
⊕⊕⊖⊖ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

⊕⊖⊖⊖ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

¹: No explanation for the observed heterogeneity could be found.

²: The wide confidence interval reflects imprecision.

Figure 22 HSROC curve for studies not reporting the threshold or not using PI-RADS for the detection of clinically significant cancer



APPENDIX H

RESULTS FROM STUDIES REPORTING PATIENTS OUTCOMES AND SAFETY OF BIOPSY

RESULTS FROM STUDIES REPORTING PATIENT OUTCOMES ASSOCIATED WITH DELAYED TREATMENT (SECTION B5)

Table 93 Summary of studies assessing impact of delayed treatment in Population 1

Study	Length of delay	Length of follow-up	N [I] N [D]	Disease risk profile	Overall survival	Cancer specific survival	Metastases Formation	Biochemical recurrence	Extra capsular extension	Lymph node positive	Positive surgical margins	Tumour upgrade
Abern et al.	[I] <9m [D] >9m	5 years	[I] 1503 [D] 58	[I] L-52%, In-48% [D] L-57% In-43%	.	.	.	37% vs. 70% (intermediate disease only)	NS	.	30% vs. 76% (intermediate disease only)	NS
Andrews et al.	[I] <3m [D1] 3-9 m [D2] >9 m	5 years	[I] 633 [D1] 623 [D2] 62	Total: L-42%, In-39%, H-19%	NS	NS	NS	NS
Dall'era et al.	[I] median 3m [D] median 18m	Median 27 months (range 1-162)	[I] 1345 [D] 63	[I] 21% low, 79% high [D] 52% low, 48% high	NS	.	NS	NS

Study	Length of delay	Length of follow-up	N [I] N [D]	Disease risk profile	Overall survival	Cancer specific survival	Metastases Formation	Biochemical recurrence	Extra capsular extension	Lymph node positive	Positive surgical margins	Tumour upgrade
Graefen et al.	[I] <1 month [D] >4 months	Mean 33 months (range 1-116)	[I] 111 [D] 42	Total: 59.6% low 36.7% int 3.7% high	.	.	.	NS
Holmstrom et al.	[I] median 3.5 months [D] median 19.2 months	Median 8 years	[I] 2344 [D] 222	Total: 100% low	NS	.	NS	25% vs. 38% p<0.001
Khan et al.	[I] <2 months [D] >2 months	10 years	[I] 162 [D] 764	Total: <5% high risk	.	.	.	NS	.	NS	.	.
Korets et al.	[I] < 2months [D1] 2-3 months [D2] >3 months	Median 64 months (IQR 30, 93)	[I] 1098 [D1] 303 [D2] 167	[I] 34% low, 54% int, 12% high [D1] 37% low, 54% int, 9% high [D2] 48% low, 47% int, 5% high	NS	.	.	NS	NS	NS	.	NS

Study	Length of delay	Length of follow-up	N [I] N [D]	Disease risk profile	Overall survival	Cancer specific survival	Metastases Formation	Biochemical recurrence	Extra capsular extension	Lymph node positive	Positive surgical margins	Tumour upgrade
Kwan et al.	[I] <3.7 months [D] >3.7 months	Median 49 months	[I] 512 [D] 512	Total 26% low, 47% int, 27% high	.	.	.	NS
Lee et al.	[I] <56 days [D] >56 days	At least 6 months	[I] 84 [D] 85	NR	NS	.
Nam et al.	[I] <3 months [D] >3 months	10 years	[I] 456 [D] 189	10.2% high risk	.	.	.	NS
Nguyen et al.	[I] <2.5 months [D] >2.5 months	5 years	[I] 240 [D] 240	9.6 % high risk	.	.	.	55% vs. 39% ($p = 0.014$), High risk disease only
O'Brien et al.	[I] <6 months [D] >6 months	Mean 38 months (range 1-222)	[I] 1052 [D] 59	100% low	.	.	NS	5% vs. 12%	NS	NS	NS	27% vs. 47%
Phillips et al.	[I] <3 months [D] >3 months	Median 2.3 years (range 0.1-14)	[I] 310 [D] 83	Total: 59% low, 25% int, 6% high	.	.	.	NS

Study	Length of delay	Length of follow-up	N [I] N [D]	Disease risk profile	Overall survival	Cancer specific survival	Metastases Formation	Biochemical recurrence	Extra capsular extension	Lymph node positive	Positive surgical margins	Tumour upgrade
Sun et al.	[I] <3 months [D] >3 months (median 11.5 months)	18 months	[I] 14577 vs. [C] 2576	100% low	NS	NS
van den Bergh et al.	[I] median 0.5 years [D] median 2.6 years	Mean 5.7 years (SD 3.2 years)	[I] 158 [D] 69	100% low	.	.	.	NS	NS	.	.	NS
Vickers et al.	[I] <90 days [D] 90-365 days	10 years	[I] 2258 [D] 891	5% high risk	.	.	.	NS
Warlick et al.	[I] median 3 months [D] median 26.5 months	10 years	[I] 150 [D] 38	100% low	.	.	NS
Redaniel et al.	[I] 0-3 months [D] 4-6 months	10 years	[I] 8522 [D] 8521	NR	NS
Eroglu et al.	NR	NR	290	NR	Delay associated with upgrade to Gleason score

Study	Length of delay	Length of follow-up	N [I] N [D]	Disease risk profile	Overall survival	Cancer specific survival	Metastases Formation	Biochemical recurrence	Extra capsular extension	Lymph node positive	Positive surgical margins	Tumour upgrade
Dong et Al.	[I] <3 months [D1] 3-6 months [D2] 6-9 months [D3] 9-24 months	Median 64 months	[I] 1611 vs. [D1] 1956 [D2] 323 [D3] 174	Total: 38% low, 40% int, 22 high	NS	.	NS	NS
Boorjian et al.	[I] <3 months [D] >3 months	5.4 years (IQR 2.2-7.9)	[I] 2258 [D] 891	[I] 67% low, 27% int, 6% high [D] 76% low, 21% int, 3% high	.	.	.	NS
O'Kelly et al.	[I] <12 months, [D1] 12-18 months, [D2] >18 months	NR	350	78.4% low 21.6% int/high	Gleason \geq 7 17% vs. 35% vs. 82%, $p < 0.001$

Study	Length of delay	Length of follow-up	N [I] N [D]	Disease risk profile	Overall survival	Cancer specific survival	Metastases Formation	Biochemical recurrence	Extra capsular extension	Lymph node positive	Positive surgical margins	Tumour upgrade
Loeb et al.	[I] <12 months, [D1] 12-24 months, [D2] >24 months	Median 8.1 years (IQR 6.6-10.1)	[I] 6864 [D1] 387 [D2] 347	[I] 70% low, 26% int, 2% high, 3% NR [D1] 59% low, 34% int, 3% high, 4% NR [D2] 47% low, 43% int, 5% high, 4% NR	.	NS	.	.	NS	.	NS	12-24 months OR 1.64 (95% CI 1.32, 2.03), > 24 months OR 2.93 (95%CI 2.34, 3.68)

I = immediate treatment group, D = delayed treatment group, NS = not significant, L = low risk disease, In = intermediate risk disease, high = high risk disease.

RESULTS FROM THE STUDIES REPORTING HARMS ASSOCIATED WITH BIOPSY (SECTION B7)

Table 94 Safety of trans-rectal biopsy

Study ID	Patients	Minor infection	Major infection	UTI	Urinary obstruction	Haematuria	Others
Anastasiadis et al. (2015) UK	198,361	.	.	1.1%	1.3%	1.4%	Hospitalisation 3.7%
Carignan et al. (2012) Canada	5,798	.	0.8%	0.8%	.	.	Hospitalisation 0.5% Bacteraemia 0.3%

Study ID	Patients	Minor infection	Major infection	UTI	Urinary obstruction	Haematuria	Others
Nam et al. (2013) Canada	75,190	0.7%	.	.	0.1%	.	Hospitalisation 1.4% Bleeding 0.2%
Roth et al. (2015) Australia	34,865	0.8%	0.09%	0.8%	0.1%	0.06%	Haematoma 0.1% Prostatitis 0.05% Fever 0.006%
Pinsky et al. (2014) USA	4,836	0.8%	.	.	0.4%	.	Death 0.4% Rectal bleeding 0.3%
Roberts et al. (2002) USA	1,776	2.7%	.	1.3%	1.9%	12.1%	Rectal bleeding 1.2% Haematospermia 0.5% Pain 2.0% Bacteraemia 0.1% Hospitalisation 0.4%
Rosario et al. (2012) UK	1,147	66.0%	Rectal bleeding 37.0% Haematospermia 93.0% Pain 44.0% Fever 20.0%
Simsir et al. (2010) Turkey	2,023	.	3.0%	.	.	.	Death 0.05%
Zaytoun et al. (2011) USA	1,438	2.2%	0.2%	.	0.8%	4.4%	Rectal bleeding 1.5% Haematospermia 0.8%
Helfand et al. (2012) USA	85	Erectile dysfunction 11.8%
Kariotis et al. (2010) Greece	434	62%	Rectal bleeding 51% Haematospermia 88%
Marino et al. (2015) USA	455	.	2.4%	1.5%	.	.	Bacteraemia 0.4% Hospitalisation 5.5%
Mohammed et al. (2016) Ireland	286	.	0.4%	.	.	.	
Petteffi et al. (2002) Brazil	105	.	.	30%, 7%	.	.	Fever 15%, 1% Hospitalisation 3.0%

Study ID	Patients	Minor infection	Major infection	UTI	Urinary obstruction	Haematuria	Others
Sahin et al. (2015) Turkey	480	6.9%	0.6%	6.2%	.	.	
Solberg et al. (2011) Norway, Sweden	875	.	.	.	21%	.	Pain 64%
Utrera et al. (2011a) Spain	220	.	.	.	Mild 24.1 %, Intense 0.9%	.	Bacteraemia 4.5% Bacteriuria 4.5% Fever 3.2% Hospitalisation 0.5%
Utrera et al. (2011b) Spain	144	.	0.7%	.	5.6%	0.7%	Prostatitis 1.4% Rectal bleeding 0.7%
Loeb et al. (2013) (Systematic review)	2,243 patients (11 studies)	27.9-63.0%	Haemospermia 6.0-13.8% Rectal bleeding 11.5-39.0% Erectile dysfunction 2.2-91.3%

UTI = urinary tract infection, . = not reported.

Table 95 Safety of trans-perineal biopsy

Study ID	Patients	Infection	Urinary obstruction	Haematuria	Hospitalisation	Mild haematuria	Others
Mai et al. (2016) China	3,007	0.03%	1.9%	47%	2.1%	0.1%	Haemospermia 6.1% Perineal haematoma 0.5% Rectal bleeding 0%
Chang et al. (2013) Systematic review	8,044 patients (34 studies)	0.0%	0.4-38.0%	0.2-57.0%	0.7-1.4%	.	UTI 1.1-8.0% Fever 1.0-5.3%
Loeb et al. (2013) Systematic review	3,203 patients (17 studies)	0.0%	1.6-20.6%	0.3-5.2%	.	3.7-45.3%	.

UTI = urinary tract infection, NR. = not reported

A search for relevant clinical trials was conducted using ClinicalTrials.gov and the Australian New Zealand Clinical Trials Registry. The identified trials are tabulated in Table 96. Sixty three trails were identified, of which 17 may provide evidence relevant to this assessment:

- Eleven included patients from Population 1, pre-biopsy patients with suspicion of PCa. These are mostly diagnostic case-control studies and two are randomised comparative studies with non-double blind assessors.
- Four included patients from Population 2, patients on AS using mpMRI for upgrading of the cancer.
- Two trials are investigating other specific populations. All males aged ≥ 50 years for a screening study (NCT02799303); and patients with negative prior biopsy in a study comparing mpMRI with TRUSGB (NCT02678481).
- The majority of trials are being conducted in the United States, Canada and the UK. There is one study relevant to this assessment that is being conducted in Australia, its time frame and finish date have not been reported.

It appears there is considerable ongoing research for the use of mpMRI of the prostate in both populations.

Table 96 Ongoing clinical trials

Study identifier, population, country	Title	Inclusion	Sponsor	Target sample size	Time frame	Status	Finish date	Study type
ACTRN126120 01137886 Population 1 Australia	Can 3-Tesla Magnetic Resonance imaging of the prostate be useful in making the decision to perform prostate biopsy in men with a high or concerning PSA?	Men with a high or concerning PSA, or abnormal prostatic rectal examination	The Wesley Hospital	225	NR	Recruiting	NR	III-3, diagnostic case-control study
NCT01492270 Population 1 UK	PICTURE - Prostate Imaging (Multi-parametric MRI and Prostate HistoScanning™) Compared to Trans-perineal Ultrasound Guided Biopsy for Significant Prostate Cancer Risk Evaluation.	Men who have undergone prior trans-rectal biopsies and are undergoing further evaluation for characterisation.	University College London Hospitals	NR	1.5 years	Unknown – status has not been verified in more than two years	NR	III-3, diagnostic case-control study
NCT02526797 Population 2 Denmark	Multiparametric MRI in Men With Prostate Cancer Undergoing Active Surveillance	Men with low risk localized PCa enrolled in active surveillance	Herlev Hospital	150	3 months	Enrolling by invitation	June 2015	III-3, diagnostic case-control study
NCT02485379 Population 1 France	Improvement in the Detection of Aggressive Prostate Cancer by Targeted Biopsies Using Multiparametric MRI Findings	Men referred for prostate mpMRI before a first set of prostate biopsies, with a planned time interval of less than 3 months	Hospices Civils de Lyon	250	1 – 4 months	Recruiting	October 2916	III-3, diagnostic case-control study
NCT02564549 Population 2 USA	Multiparametric MRI-Based Active Surveillance to Avoid the Risks of Serial Biopsies in Men With Low-Risk Prostate	Gleason score ≤ 6	Virginia Commonwealth University, Massey Cancer Center, Hunter	192	3 years	Recruiting	October 2017	III-2

Study identifier, population, country	Title	Inclusion	Sponsor	Target sample size	Time frame	Status	Finish date	Study type
	Cancer (MAVERICK)		Holmes Mcguire Veteran Affairs Medical Center					
NCT01292291 Population 1 UK	PROMIS - Prostate MRI Imaging Study - Evaluation of Multi-Parametric Magnetic Resonance Imaging in the Diagnosis and Characterization of Prostate Cancer	Men at risk of PCa who have been advised to have a prostate biopsy	University College London Hospitals	714	NR	Not yet recruiting	April 2013	III-3, diagnostic case-control study
NCT01858688 Population 1 USA	A Phase II, Prospective Study of MRI in the Reclassification of Men Considering Active Surveillance in Prostate Cancer	Men with histologically confirmed PCa with all of the following features: Min. 10 core prostate biopsy showing histologically-confirmed PCa within 12 months of enrolment; Gleason $\leq 3+3$; No tertiary Gleason grade ≥ 4 ; ≤ 3 total cores positive; $\leq 50\%$ of any given core involved with cancer; No evidence on biopsy of extracapsular extension; PSA within one month of enrolment: < 10 ng/mL; Clinical stage: $\leq T2a$ & N0 or NX & M0	Dana-Farber Cancer Institute	130	2 years	Recruiting	July 2018	III-3, diagnostic case-control study
NCT02388126 Population 1/Other Finland	Prostate Magnetic Resonance Imaging in Patient With Previous Negative Biopsies (PROMANEG)	Men with clinical suspicion of PCa and/or previous negative prostate biopsies	Turku University Hospital	150	3 months	Recruiting	February 2016	III-3, diagnostic case-control study

Study identifier, population, country	Title	Inclusion	Sponsor	Target sample size	Time frame	Status	Finish date	Study type
NCT02799303 Other Canada	A Randomized Clinical Trial Comparing the Efficacy of MRI Versus PSA for Prostate Cancer Screening: The MVP Study (MRI vs PSA)	≤ 50 years of age	Sunnybrook Health Sciences Centre	NR	3 years	Not yet open for recruitment	June 2020	III-2
NCT02721784 Population 2 UK	Serial mpMRI Scanning in Prostate Cancer After Androgen Deprivation Therapy and RadioTherapy (SMART)	Men with biopsy confirmed PCa who had mpMRI scan of the prostate pre-biopsy	University College, London	10	6 months	Not yet open for recruitment	January 2018	III-3, diagnostic case-control study
NCT02524860 Population 1 Canada	Targeted Prostate Biopsy Using a Novel MRI-Ultrasound Fusion Device in Patients With an Elevated PSA and a Positive Multiparametric MRI	Candidates for fusion biopsy; Elevated PSA levels; mpMRI with lesions having a Prostate Imaging Reporting and Data System (PI-RADS) score greater than or equal to 3	Focal Healthcare Inc.	NR	1 year	Not yet open for recruitment	July 2016	III-3, diagnostic case-control study
NCT02380027 Population 1 UK	PRostate Evaluation for Clinically Important Disease: Sampling Using Image-guidance Or Not? (PRECISION)	Suspicious PSA and DRE	University College, London	470	1 month	Recruiting	September 2017	III-2, single blind RCT
NCT02745496 Population 1 UK	Multiparametric Magnetic Resonance Imaging Characterization and Guided Biopsy of the Prostate in Men Suspected of Having Prostate Cancer	Men aged 40-75 years, with suspicious PSA and/or DRE	University of Dundee	600	4 years	Recruiting	January 2019	III-2
NCT02678481 Other Italy	MR-targeted vs. Random TRUS-guided Prostate Biopsy in Patients With	Patients with negative biopsy	Fondazione del Piemonte per l'Oncologia	90	3 months	Recruiting	August 2016	III-2

Study identifier, population, country	Title	Inclusion	Sponsor	Target sample size	Time frame	Status	Finish date	Study type
	High PSA Values and Previous Negative Biopsy Results: A Randomized Controlled Trial							
NCT01354171 Population 2 Canada	Active Surveillance Magnetic Resonance Imaging Study (ASIST)	Candidate for active surveillance	Canadian Urology Research Consortium	250	1 year	Unknown – status has not been verified in more than two years	September 2014	III-2
NCT02053805 Population 1 Israel	Personalized Prostate Cancer Screening Among Men With High Risk Genetic Predisposition- a Prospective Cohort Study	Male carrier of mutation in BRCA 1/2 or germ-line mutations in the MMR genes (MLH1, MSH2, MSH6 or PMS2)	Rabin Medical Center	200	2 years	Recruiting	June 2018	III-3, diagnostic case-control study, screening population
NCT02326246 Population 2 Denmark	Multi-parametric MRI in the Diagnosis and Surveillance of Low-risk Prostate Cancer	Men with low-risk PCa	Aarhus University Hospital Skejby	60	1 year	Recruiting	February 2017	III-3, diagnostic case-control study

NR = not reported, PCa = prostate cancer, MRI = magnetic resonance imaging, RCT = randomised controlled trial, mpMRI = Multiparametric MRI.

A search for relevant clinical practice guidelines was conducted using major depositories of clinical guidelines, including Agency for Healthcare Research and Quality (AHRQ), Clinical Practice Guidelines Portal by National Health and Medical Research Council (NHMRC), National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN), EuroScan International Network, York Centre for Reviews and Dissemination, and Trip database. Manual searches using the Google search engine were also performed. Search strategies were designed around the keyword terms including “prostate cancer”, “cancer detection”, and “mpMRI”. The identified guidelines are listed in Table 97.

The search identified four guidelines relevant to the detection and characterisation of prostate lesions using mpMRI.

Cancer Council Australia offers a guideline, updated this year, on testing and early management of test-detected PCa. It suggests mpMRI be considered for men with a negative TRUSGB to determine whether another biopsy is needed. Another biopsy should not be offered if mpMRI is negative, unless any of the following risk factors are present:

- atypical small acinar proliferation on initial biopsy
- abnormal digital rectal examination before the initial biopsy
- high-grade prostatic intraepithelial neoplasia on initial biopsy.

mpMRI should be used only in centres with experienced radiologists appropriately trained in the use of multiparametric MRI to aid urologists in the management of individual patients.

For patients under AS mpMRI is recommended in centres where staff have skills and experience it use for prostate examination. Clinicians should consider using mpMRI to help identify foci of potentially higher-grade disease, aid targeting at reclassification biopsies and aid in determination of interval tumour growth. Clinicians and other staff performing mpMRI should refer to appropriate standards and guidelines for its use.

The guideline states ‘This guideline focuses on the use of mpMRI after a negative prostate biopsy, not on its use for the primary investigation of a positive PSA test, because this is not routine clinical practice. The use of mpMRI in men with elevated PSA levels who have not yet undergone an initial biopsy is beyond the scope of this guideline.’

Cancer Care Ontario has published recommendations on mpMRI in the diagnosis of PCa (Cancer Care Ontario 2015). It is suggested mpMRI followed by target biopsy should not be considered the standard of care for biopsy naïve men with elevated PSA levels; and that data from future research studies are essential to determine the value of mpMRI in this clinical context. Further, it suggested

the patient should be informed of the possibility of false-negative results from TRUSGB. In patients who had a prior negative TRUS-guided systematic biopsy and demonstrate a growing risk of having clinically significant PCa mpMRI followed by targeted biopsy may be considered to help in detecting more clinically significant PCa patients compared with repeated TRUS-guided systematic biopsy.

NICE has also published guidelines including the use of mpMRI in PCa detection. It suggests mpMRI should be considered for men with negative TRUSGB to determine whether another biopsy is needed. Another biopsy should not be offered if the mpMRI is negative unless one of the following risk factors is present:

- the biopsy showed high-grade prostatic intra-epithelial neoplasia (HGPIN)
- the biopsy showed atypical small acinar proliferation (ASAP)
- the patient has abnormal digital rectal examination.

For patients in AS, mpMRI should be conducted on enrolment in AS if not previously performed.

The American College of Radiology publishes Appropriateness Criteria, which are evidence-based guidelines for specific clinical conditions with a modified Delphi methodology; this Appropriateness Criteria encompasses detection staging and surveillance of prostate biopsy. It is hesitant to make specific recommendations on mpMRI but claims that international evidence is amalgamating around this approach for imaging PCa.

Table 97 Relevant clinical guidelines for mpMRI in prostate biopsy for cancer detection

Title (year)	Author	Website	Summary
PSA testing and early management of test-detected prostate cancer (2016)	Cancer Council Australia	www.cancer.org.au	Does not suggest mpMRI for biopsy naïve men. Suggests mpMRI for those with negative biopsy to see if another biopsy is needed.
Multiparametric Magnetic Resonance Imaging in the Diagnosis of Clinically Significant Prostate Cancer (2015)	Cancer Care Ontario	www.cancercare.on.ca	Does not suggest mpMRI for biopsy naïve men. Suggests mpMRI for those with negative biopsy to see if another biopsy is needed.
Prostate cancer: Diagnosis and treatment (2014)	NICE	www.nice.org.uk	Does not suggest mpMRI for biopsy naïve men. Suggests mpMRI for those with negative biopsy to see if another biopsy is needed.
ACR Appropriateness Criteria Prostate Cancer—Pretreatment Detection, Staging, and Surveillance (2013)	American College of Radiology	www.acr.org	Does not suggest mpMRI for biopsy naïve men. Suggests mpMRI for those with negative biopsy to see if another biopsy is needed.

mp-MRI = multiparametric MRI, PSA = Prostate specific antigen.

LITERATURE SEARCH FOR SECTION D.3: ECONOMIC EVALUATIONS

Simpler search strings were constructed for the search of websites of HTA agencies due to the fewer number of results generated. In both searches conducted, studies were included for further review if they included:

- 1) A population of men with;
 - a. Suspected prostate cancer; or
 - b. Low to intermediate risk prostate cancer, undergoing active surveillance.
- 2) Included medical services of: mpMRI and/or MRIGB and/or TRUSGB/TPUSGB.
- 3) An economic evaluation consisting of a cost analysis, cost-effectiveness analysis or a cost-utility analysis.

The searches were conducted on the 25th of June 2016. A summary of the search results of the HTA websites are provided in Table 98 and results of the PubMed search are provided in Table 99.

Table 98 Search of health technology websites

Organisation	Search Strings (articles found)	Relevant Documents
Canadian Agency for Drugs and Technologies in Health https://www.cadth.ca/	multiparametric magnetic resonance imaging = 2 Prostate cancer = 134	1 ^a
Pharmacology and Therapeutics Advisory Committee (Pharmac: Pharmaceutical Management Agency) https://www.pharmac.govt.nz/	multiparametric magnetic resonance imaging = 1 Prostate cancer = [7 web pages reviewed]	0
Scottish Medicine Consortium www.scottishmedicines.org.uk	multiparametric magnetic resonance imaging = 5 Prostate cancer = 13	0
National Institutes of Health and Clinical Excellence www.nice.org.uk	multiparametric magnetic resonance imaging = 6 Prostate cancer = 211	1 ^b
Centre for Reviews and Dissemination (encompassing the Database of Abstracts of Reviews of Effects – DARE, the NHS Economic Evaluation Database – NHS EED, and the Health Technology Assessment Database – HTA) https://www.york.ac.uk/crd/	multiparametric magnetic resonance imaging = 0 Prostate cancer = 8	0

Notes: All above sites accessed on-line on 25th June 2016.

^a: CADTH: <https://www.cadth.ca/sites/default/files/pdf/htis/feb-2014/RB0648%20MRSI%20for%20Prostate%20Disease%20Final.pdf>;

^b: NICE: Prostate cancer: diagnosis and management CG175 <https://www.nice.org.uk/guidance/cg175>;

PubMed Search strategy: Search (((((Economic analys*[Text Word]) OR (Economic evaluation*[Text Word]) OR (Economic model*[Text Word]) OR (Cost effective*[Text Word]) OR (Cost minimi*[Text Word]) OR (Cost utilit*[Text Word]) OR (Health economics[Text Word]) OR (Quality adjusted life

year*[Text Word]) OR (QALY*[Text Word]) OR (Life year* AND saved[Text Word]) OR (Life year* AND gained[Text Word])) OR ((models, economic[MeSH Terms]) OR (Quality adjusted life years[MeSH Terms]) OR (Economics, pharmaceutical[MeSH Terms]))) AND (((((prostate) OR prostate[MeSH Terms])) AND (((((((((((multiparametric magnetic resonance imaging) OR multiparametric MRI) OR multiparametric-MRI) OR MP-MRI) OR MP MRI) OR MPMRI) OR MP-magnetic resonance imaging) OR MP magnetic resonance imaging)) OR (((((((diffusion weighted) OR DW) OR diffusion-weighted)) AND dynamic) AND T1) AND T2) AND (((MRI) OR magnetic resonance imaging) OR magnetic resonance imaging[MeSH Terms])))

Table 99 Results of PubMed literature search: economic evaluations [search date 25th of June 2016]

Inclusion/exclusion criteria	No citations
Total	16
Not specific for mpMRI in prostate cancer or prostate cancer screening or clinical management	0
Not an economic evaluation	11
Total excluded	11
Manual find	1
Include	6 ^a

^a: Included citations: (de Rooij et al. 2014; Gordon et al. 2016; Lotan et al. 2015; Mowatt et al. 2013; Nicholson et al. 2015)

LITERATURE SEARCH FOR SECTION D.4: AUSTRALIAN COST STUDIES

A simple search string was constructed for the targeted literature search of PubMed. The search aimed to identify costs studies conducted in Australia. Studies were included for further review if they included:

- 1) The publication was an original study reporting the outcome of costs due to prostate cancer. Costs reported from the healthcare perspective.
- 2) The study was conducted in Australia; and
- 3) The study included a population of men with;
 - a. Suspected prostate cancer; or
 - b. Low to intermediate risk prostate cancer, undergoing active surveillance.

PubMed Search strategy: (((costs) OR costs[MeSH Terms])) AND (((prostate) OR prostate cancer[MeSH Terms])) AND Australia).

The search was conducted on the 14th of July 2016. A total of 49 citations were reviewed to determine applicability of the costs to the economic model. A manual search was also conducted of the grey literature. The search was restricted to studies published after 2000.

Table 100 Results of PubMed literature search: Australian cost studies [search date 14th of July 2016]

Inclusion/exclusion criteria	No citations
Total	49
A) Does not report costs	24
B) Study was not conducted in Australia	4
C) Study is not specific for prostate cancer [including description of treatments/diagnostics in the clinical management algorithm]	6
D) Study does not report costs from a healthcare perspective	15
Total excluded	49
Manual inclusion [expert consultation]	1
Include	1 ^a

^a Included citations: Cronin et al 2016. This publication has recently been accepted for publication in the Asia-Pacific Journal of Clinical Oncology (Manuscript ID APJCO-2015-0513.R1). A draft manuscript was provided by the author, however, the publication is still unavailable in the public domain.

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