Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1424 – MR guided biopsy procedures for diagnosis of prostate cancer

Applicant: **Australian and New Zealand Association of Urological Surgeons**

Date of MSAC consideration: **MSAC 69th Meeting, 6-7 April 2017**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1. Purpose of application

An application requesting two new Medicare Benefits Schedule (MBS) listings for MR-guided prostate biopsy in men with a high or concerning Prostate Specific Antigen (PSA) and under suspicion of harbouring prostate cancer was received from the Australian and New Zealand Association of Urological Surgeons (ANZAUS) and the Australian Diagnostic Imaging Association (ADIA) by the Department of Health (the Department).

2. MSAC's advice to the Minister

After considering the strength of the available evidence presented in relation to comparative safety, clinical effectiveness and cost-effectiveness MSAC did not support MBS listing of magnetic resonance imaging (MRI)-guided biopsy procedures for the diagnosis of prostate cancer. MSAC accepted that MRI-guided biopsy procedures for the diagnosis of prostate cancer are safe and have acceptable diagnostic accuracy in comparison with ultrasound-guided biopsy procedures. MSAC noted however that the cost-effectiveness of the proposed procedures were highly uncertain and that the proposed MBS fees were inadequately justified.

Any resubmission would need to (a) revise the estimated costs for the comparator and the two MRI-associated biopsy procedures, (b) provide input based justifications for these revised costs and (c) recalculate the economic model and financial implications based on the revised costings.

MSAC advised that any resubmission would need to be considered by ESC.

3. Summary of consideration and rationale for MSAC's advice

MSAC considered an application requesting MBS listing of the following MRI-guided biopsy procedures for the diagnosis of prostate cancer:

- Magnetic resonance (MR)-in gantry: A procedure typically performed using a transrectal approach within the bore (gantry) of the magnet, requiring MR-compatible equipment. This method allows the position of the biopsy needle to be directly validated within the identified lesion on multiparametric MRI (mpMRI); and
- MR-ultrasound (US) fusion: A procedure performed with either transrectal ultrasound guided biopsy (TRUSGB) or transperineal ultrasound guided biopsy (TPUSGB) using software fusion of previously acquired mpMRI images and ultrasound images. This method provides real-time ultrasound guidance but does not allow validation of the track of the biopsy needle through the identified mpMRI lesion as the MRI image is not live.

MSAC noted that the application proposed these procedures would be used exclusively for the diagnosis of prostate cancer in patients who are likely to be at intermediate/high risk of the disease. MSAC considered the following two patient populations as noted in the application:

- Population 1: men who are suspected of having prostate cancer on the basis of a Prostate Imaging Reporting and Data System (PI-RADS) 4–5 lesion on diagnostic mpMRI; and
- Population 2: men undergoing active surveillance for prostate cancer who develop a PI-RADS 4–5 lesion on diagnostic mpMRI.

MSAC noted that cognitive TPUSGB, which involves a review of previous mpMRI images and real-time ultrasound guidance (without fusion), was updated as the main comparator based on advice from the applicant that this approach is now established in clinical practice in Australia. MSAC noted that systematic TRUSGB/TPUSGB is still performed and is nominated as a supportive comparator.

MSAC noted that the proposed clinical management algorithm involves the replacement of the comparator biopsy procedures with either MR-in gantry or MR-US fusion. In considering the key differences between the biopsy procedures MSAC noted the applicant's advice that MR-in gantry and MR-US fusion require fewer needles (2 to 4 core) than their comparators (e.g. cognitive TPUSGB requires up to 10 cores). MSAC also noted that in contrast with MR-US fusion or cognitive TPUSGB which are performed under general anaesthesia and require patient admission into day theatre (procedure time: 1 hour), MR-in gantry is performed within imaging departments (procedure time: <30 minutes).

MSAC noted that no direct evidence regarding the safety of MR-in gantry or MR-US fusion in comparison with cognitive TPUSGB or systematic TRUSGB/TPUSGB was identified. The evaluation of safety was instead based on evidence for TRUSGB and TPUSGB alone. MSAC noted that minor complications (i.e. haematuria, haematospermia and rectal bleeding) are common with these procedures, though generally transient and self-limiting. Examples of major complications included severe infection (urosepsis/sepsis) and severe rectal bleeding. MSAC noted that these adverse events were often associated with the method of approach (i.e. whether transrectal or transperineal). Where a transrectal approach is used, MSAC accepted that it is reasonable to assume that the risk of infection is proportional to number of biopsy needles required.

In considering the comparative evidence included in the application to support the effectiveness of the proposed services, MSAC questioned whether the exclusion of two studies involving MR-US fusion (Cool DW et al, 2015 and Marks L et al, 2013) was appropriate. MSAC noted that a linked evidence approach was used as no direct evidence

regarding the effectiveness of MR-in gantry or MR-US fusion in comparison to the nominated comparators met inclusion criteria.

MSAC agreed that according to this evidence, both MR-in gantry and MR-US fusion had similar diagnostic accuracy to cognitive TPUSGB, with higher levels of sensitivity in population 1 specifically. MSAC noted that there was limited evidence for population 2 for cognitive TPUSGB.

Relative to systematic TRUSGB/TPUSGB, MSAC considered that both MR-in gantry and MR-US fusion outperform this comparator in terms of diagnostic accuracy with a significantly higher sensitivity but similar specificity in population 1. MSAC noted that evidence was not available for MR-in gantry for population 2. MSAC accepted that available evidence for MR-US fusion indicates this procedure outperforms systematic TRUSGB/TPUSGB with significantly higher sensitivity but similar specificity in population 2.

MSAC noted data indicating higher reclassification rates in men undergoing active surveillance for prostate cancer using MR-in gantry and MR-US fusion compared with standard TRUSGB. MSAC noted that the evidence for the impact of delayed treatment in men with a false negative result was mixed.

Based upon the limited evidence available, MSAC concluded that MR-in gantry and MR-US fusion appear to have at least non-inferior safety and superior effectiveness to their comparators.

MSAC noted that one lifetime economic model comparing MR-in gantry and MR-US fusion with cognitive TPUSGB was presented in the application for population 1 (model 1). MSAC noted that, due to the limited clinical evidence regarding the diagnostic accuracy of the biopsy procedures in comparison with cognitive TPUSGB in population 2, no economic model was presented for this group.

MSAC noted that in the base case for model 1, it was assumed that the costs of the cognitive TPUSGB, MR-US fusion and MR-in gantry biopsy procedures were $925.72, $1,149.72 and $2,375.11, respectively. The model generated incremental cost effectiveness ratios (ICERs) of $163,993 per QALY and $31,011 per QALY for MR-in gantry and MR-US fusion, respectively compared to cognitive TPUSGB. MSAC considered the results of sensitivity analyses conducted and noted that the ICER for MR-US fusion was sensitive to a range of inputs including biopsy costs.

MSAC noted that in their Pre-ESC response, the applicant advised that the cost of cognitive TPUSGB used in the base case for model 1 was below the current cost for the procedure and requested that the cost of all MR-guided biopsy procedures reflect the current market price. In turn, these costs were increased in the assessment group rejoinder to $4,100, $4,100 and $2,600 for cognitive TPUSGB, MR-US fusion and MR-in gantry, respectively. In addition, the assumption of disease upgrading for those whose intermediate/high-risk cancer was missed with initial biopsy was removed. MSAC noted that these changes resulted in MR-in gantry and MR-US dominating cognitive TPUSGB and was concerned that their cost-effectiveness relies heavily upon the assumed cost of the comparator. MSAC questioned the validity of using estimated current market prices in the economic model. MSAC concluded that a revision of the estimated biopsy costs was required and that input-based justifications should be provided.

MSAC also considered the economic models in which systematic TRUSGB/TPUSGB was the comparator for population 1 (model 2) and population 2 (model 3). Biopsy procedure costs of $651.33, $875.33 and $2,375.11 were used for systematic TRUSGB/TPUSGB, MR-

US fusion and MR-in gantry, respectively. For population 1 the ICER for MR-in gantry and MR-US fusion were $56,267 per QALY and $5,000 per QALY, respectively. For population 2, the ICER for MR-in gantry was $47,985 per QALY and $1,474 per QALY for MR-US fusion.

In considering the financial impact of the proposed procedures, MSAC noted that using the base case outlined in the application, the listing of the two MRI-guided biopsies would result in an estimated cost to the MBS of $18.5 million over five years. MSAC was concerned that the estimated costs to the MBS increased to $20.0 million over five years if the biopsy procedure costs used in the rejoinder were used. MSAC was also concerned that when the costs to other government health budgets were included, the results varied from a cost impact to the wider Australian healthcare system to a cost saving, depending on the input biopsy procedure cost.

MSAC concluded that it did not support public funding of MRI-guided biopsy procedures for the diagnosis of prostate cancer as the cost-effectiveness was highly uncertain and the proposed MBS fees were inadequately justified.

MSAC foreshadowed that any resubmission would need to:

- revise the estimated costs for the comparator and the two MRI-guided biopsy procedures;
- provide input based justifications for these revised costs; and
- recalculate the economic model and financial implications based on the revised costings.

4. Background

The initial application (1397: Prostate MRI) was reviewed by the Protocol Advisory Sub-committee (PASC) in April 2015 and August 2015. PASC advised that the initial application should be spilt into two applications:

1. Intervention for Diagnostic mpMRI; and
2. Intervention for MR-guided biopsy.

There is now a separate application for mpMRI prostate diagnostic scans for diagnosis of prostate cancer (MSAC application 1397) and MR-guided biopsy procedures for diagnosis of prostate cancer (MSAC application 1424).

MSAC also considered Application 1397 at its April 2017 meeting. Further information can be found in the Public Summary Document on the MSAC website.

5. Prerequisites to implementation of any funding advice

MRI systems are registered with the Therapeutic Goods Administration (TGA) on the Australian Register of Therapeutic Goods (ARTG).

6. Proposal for public funding

Two MBS items are proposed, one for MR-in gantry (

Table 1) and one for MR-US fusion (Table 2).

Table 1 Proposed MBS item descriptor for MR-in gantry

Category 3 – Therapeutic procedures
MBS [item number] Magnetic Resonance Imaging-guided prostate biopsy, using an MRI machine in real time (MRGB) in men who are suspected of having prostate cancer on the basis of the mpMRI scan (PI-RADS 4 or PI-RADS 5). Fee: Applicant advises that current fee charged for MRGB is $2300 [a] [Relevant explanatory notes] A limit of one MRI-guided biopsy per patient per 12 month period, to be accessed by referral from a specialist (e.g. urologist, radiation oncologist or medical oncologist).

mp = multiparametric; MRGB (MR-in gantry) = In gantry magnetic resonance guided biopsy; MRI = magnetic resonance imaging; PI-RADS = Prostate Imaging- Reporting and Data System;
[a] The proposed fee for MRGB (MR-in gantry) consists of: MRI time ($800), disposables ($650), and professional fee for urologist or radiologist ($850)

The application indicated the cost of MR-in gantry at $2,300 was estimated from private fees used in practice in Australia. The proposed fee for MR-in gantry is much higher compared with MR-US fusion ($389.95). For context of the proposed fee of MR-in gantry, the MBS fee for MRI-guided breast biopsy (item 63489) is $1,440.00 (85% is $1359.80).

Table 2 Proposed MBS item descriptor for MR-US fusion

Category 3 – Therapeutic procedures
MBS [item number] Magnetic Resonance Imaging-guided prostate biopsy, using previously acquired magnetic resonance images which are fused using an ultrasound machine, in men who are suspected of having prostate cancer on the basis of the mpMRI scan (PI-RADS 4 or PI-RADS 5). Fee: $280.85 (Anaes.) [Relevant explanatory notes] A limit of one MRI-guided biopsy per patient per 12 month period, to be accessed by referral from a specialist (e.g. urologist, radiation oncologist or medical oncologist).
Category 5– Diagnostic procedures
MBS [item number] PROSTATE, bladder base and urethra, ultrasound scan of, where performed: (a) personally by a medical practitioner who undertook the assessment referred to in (c) using a transducer probe or probes that: (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 (ii) can obtain both axial and sagittal scans in 2 planes at right angles; and (b) following 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 or a consultant physician in medical oncology who has: (i)examined the patient in the 60 days prior to 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

mp = multiparametric; MRI = magnetic resonance imaging; PI-RADS = Prostate Imaging- Reporting and Data System.

The applicant indicated that the current fees used for cognitive TPUSGB (MBS item 37219) and ultrasound (MBS item 55603) was used to estimate the cost of MR-US fusion. It was noted the applicant did not propose a fee for the fusion software required to perform MR-US fusion.

7. Summary of Public Consultation Feedback/Consumer Issues

The Protocol Advisory Sub-Committee (PASC) received seven responses from peak bodies, three responses from organisations, six responses from specialists, one response from a researcher and three responses from consumers.

Issues raised in the responses were:

- Specialist referral should be required from an urologist, radiation oncologist, or medical oncologist.
- MR assisted (cognitive fusion, US fusion) TRUS and TPB is already being done under the existing biopsy item numbers and the bulk of members are satisfied with the current arrangements and are happy continuing to utilise these numbers for this purpose despite it taking longer.
- The adverse outcomes of biopsy are overstated here as there is a growing trend to trans-perineal biopsies in Australia that have a close to 0% risk of sepsis.
- The feasibility of measuring change in overall survival and change in prostate cancer specific mortality is very doubtful for a cancer with such a long natural history as prostate cancer (typically >10 years from diagnosis to death).
- The savings in pathology costs are likely to be insignificant compared to the additional cost of MRGB.

8. Proposed intervention's place in clinical management

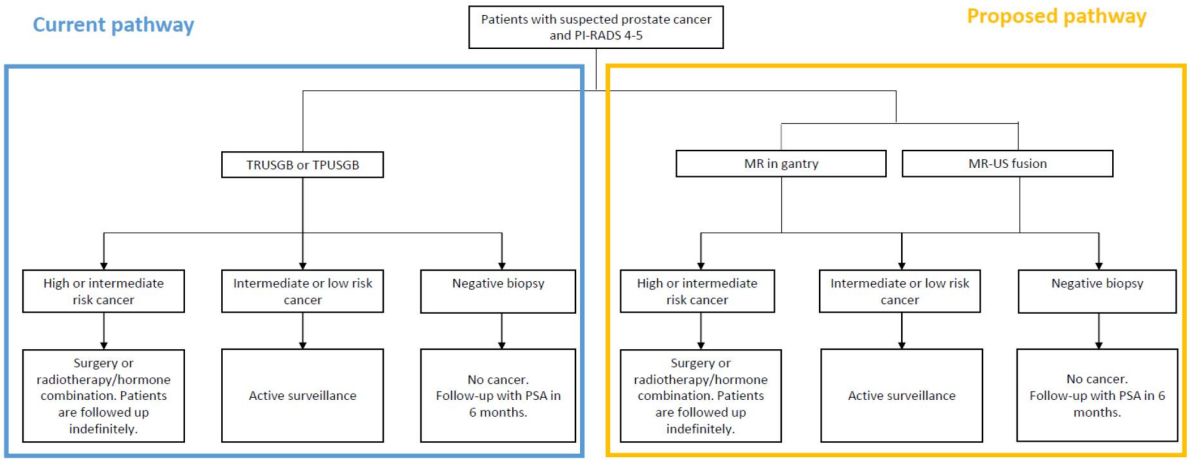
The proposed medical services are for two MRI-guided biopsy procedures:

1. MR-in gantry which is performed within the bore (gantry) of the magnet, and therefore requires MR-compatible equipment. MR-in gantry is performed in specialised medical imaging departments and does not require hospital admission; and
2. MR-US fusion which can be performed either with transrectal ultrasound-guided biopsy (TRUSGB) or transperineal ultrasound-guided biopsy (TPUSGB) using software fusion of previously acquired multiparametric (mp) MRI images with ultrasound images. MR-US fusion, if performed with TPUSGB (general anaesthesia) is performed in day theatre and therefore requires hospital admission.

Population 1: Men suspected of prostate cancer (undiagnosed)
The proposed clinical management algorithm for men suspected of prostate cancer (

Figure 1) states that men with PI-RADS 4-5 lesion on baseline mpMRI would undergo either MR-in gantry or MR-US fusion, and will be offered the same management options as under the current clinical management algorithm (described below).

Figure 1 Current and proposed clinical management algorithm for men suspected of PCa (Population 1)

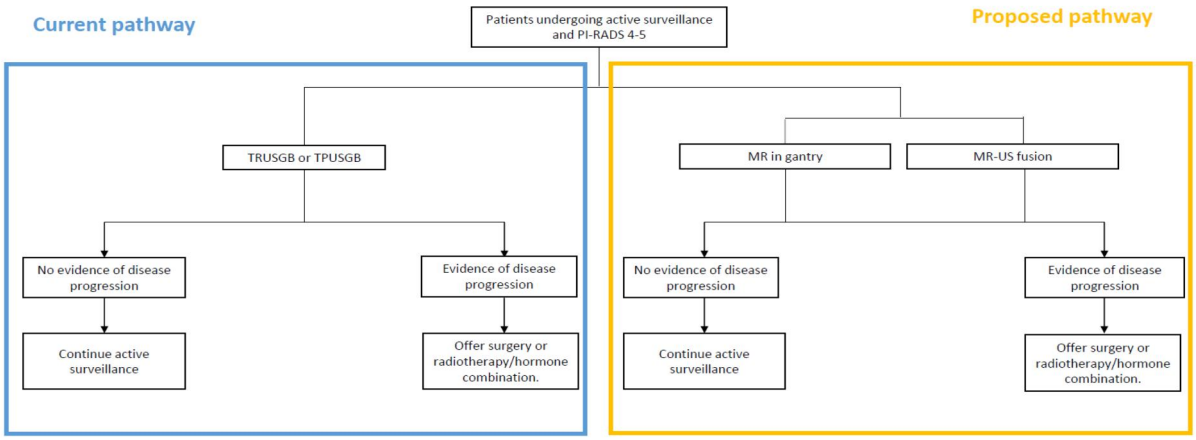


PCa = prostate cancer; PI-RADS = Prostate Imaging-Reporting and Data System; PSA = proton specific antigen; TPUSGB = transperineal ultrasound-guided biopsy; TRUSGB = transrectal ultrasound-guided biopsy

Population 2: Men diagnosed with prostate cancer undergoing active surveillance

The proposed clinical management algorithm for men undergoing active surveillance for prostate cancer (Figure 2) states that men classified as PI-RADS 4-5 on mpMRI will undergo either MR-in gantry or MR-US fusion and are offered the same management options as under the current clinical management algorithm (described below).

Figure 2 Current and proposed clinical management algorithm for men with PCa undergoing AS



AS = active surveillance; PCa = prostate cancer; PI-RADS = Prostate Imaging-Reporting and Data System; PSA = prostate specific antigen; TPUSGB = transperineal ultrasound-guided biopsy; TRUSGB = transrectal ultrasound-guided biopsy

9. Comparator

For **MR-in gantry** (intervention 1), the nominated comparators are:

1. Main comparator (contemporary): Cognitive TPUSGB is defined as ultrasound-guided biopsy via cognitive (targeted) approach (with mpMRI guidance). This is used as the main clinical comparator and the main economic comparator in the assessment report.
2. Supportive comparator (historical): TRUSGB/TPUSGB (for diagnosing prostate cancer) defined as ultrasound-guided biopsy via systematic (random) approach

(without mpMRI guidance). This is used as the supportive clinical comparator in the assessment report.

For **MR-US fusion** (intervention 2), the nominated comparators are:

1. Main comparator (contemporary): Cognitive TPUSGB is defined as ultrasound-guided biopsy via cognitive (targeted) approach (with mpMRI guidance). This is used as the main clinical comparator and the main economic comparator in the assessment report.
2. Supportive comparator (historical): TRUSGB/TPUSGB (for diagnosing prostate cancer) defined as ultrasound-guided biopsy via systematic (random) approach (without mpMRI guidance). This is used as the supportive clinical comparator in the assessment report.

10. Comparative safety

There was limited comparative evidence on safety of MR-in gantry or MR-US fusion versus TRUSGB/TPUSGB. A retrospective survey (n=54) compared complications (and their severity) associated with MR-in gantry versus TRUSGB/TPUSGB (level of evidence = IV) (Egbers et al. 2015). The results showed that the most common side-effects of both biopsy techniques were haematuria, followed by haemospermia and rectal haemorrhage. Only haematuria was significantly higher after TRUSGB compared with MR-in gantry (79% vs. 51%, respectively; p=0.006). The results showed that the major complication rate was low for both biopsy procedures (<6%; 3/54). Of these, there was one case of infection with fever (2%) for MR-in gantry compared with two cases (4%) for TRUSGB/TPUSGB. The authors suggested that the lower rate of complications associated with MR-in gantry might be associated with the smaller number of punch biopsies.

Overall, major complications are not reported frequently (<1%) with MR-in gantry or MR-US fusion. As MR-in gantry or MR-US fusion use fewer cores compared with TRUSGB/TPUSGB, it could be reasonable to assume that the incidence of infection (using a transrectal approach) could be proportional to the number of cores taken. From Toner *et al.* 2016, a recent study concluded that the number of biopsy needles is proportional to the infection risk with a transrectal approach. Expert opinion advised us that this could be a reasonable assumption as it would seem logical that the chance of inoculation of enteric bacteria into the blood stream via a rectal biopsy is proportional to the number of times a rectal inoculation occurs. However, this has yet to be proven in clinical trials on MR-in gantry or MR-US fusion versus TRUSGB/TPUSGB.

11. Comparative effectiveness

No studies on the direct effectiveness of MR-in gantry or MR-US fusion compared with cognitive TPUSGB (or systematic TRUSGB/TPUSGB) were identified. The comparison of MR-in gantry or MR-US fusion with cognitive TPUSGB was through an indirect comparison (common comparator: systematic TRUSGB/TPUSGB).

Diagnostic accuracy (including clinical validity)

MR-in gantry and MR-US fusion in men suspected of Prostate Cancer

A summary of the diagnostic accuracy of MR-in gantry and MR-US fusion for men suspected of prostate cancer relative to cognitive TPUSGB is provided in Table 3.

Table 3 Summary of findings for the accuracy of MR-in gantry and MR-US fusion, relative to cognitive TPUSGB, including patients classified as PI-RADS 4-5, with an assumed pre-test probability (prevalence) of intermediate/high-risk cancer at 89% (men suspected of PCa) [a]

Outcomes	Participants	Proposed Intervention 1	Proposed Intervention 2	Intervention 3 [b]	Quality of evidence	Comments
—	—	**MR-in gantry [95%CI]**	**MR-US fusion [95%CI]**	**Cognitive (MR) [c] TPUSGB [95%CI]**	—	—
Sensitivity	Mixed population	0.92 (0.76-0.98)	0.89 (0.82-0.93)	0.86 (0.69 – 0.94)	⊕⊕⊕⊕	Wegelin 2016 Level III-1

[*] GRADE Working Group grades of evidence (Guyatt *et al*. 2013)
CI = confidence interval; MR = magnetic resonance; PI-RADS = Prostate Imaging-Reporting and data System; TRUSGB = transrectal ultrasound-guided biopsy; US = ultrasound
⊕⊕⊕⊕ **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.
[a] All MR-guided biopsy procedures were compared with systematic TRUSGB/TPUSGB (reference standard = biopsy specimens)
[b] Nominated main comparator
[c] Of 3 studies included for cognitive biopsy, 1 study used TPUSGB approach

The results showed that MR-in gantry had the highest sensitivity for intermediate/high-risk cancer at 92% (95% confidence interval (CI): 0.76 to 0.98); compared with MR-US fusion at 89% (95% CI: 0.82 to 0.93); and cognitive TPUSGB at 86% (95% CI: 0.69 to 0.94).

A summary of the diagnostic accuracy of MR-in gantry and MR-US fusion for men suspected of prostate cancer is provided in Table 5Table 4 (compared with systematic TRUSGB/TPUSGB).

Table 4 Summary of findings for the accuracy of MR-in gantry and MR-US fusion, relative to systematic TRUSGB/TPUSGB, including patients classified as PI-RADS 4-5, with an assumed pre-test probability (prevalence) of intermediate/high-risk cancer at 89% (men suspected of PCa)

Outcomes	Participants	Intervention	Supportive comparator	Quality of evidence	Study, level of evidence, n
—	—	**MR-in gantry [95%CI]**	**Systematic TRUSGB [95%CI]**	—	—
Sensitivity	Biopsy naive, PI-RADS	0.90 (0.83-0.95)	0.72 (0.62 – 0.80)	⊕⊕⊕⊕	Schoots 2015, Level III-2, n=1,657
Specificity	Biopsy naïve, PI-RADS	0.97 (0.93- 0.99)	0.94 (0.89- 0.96)	⊕⊕⊕⊙	Pokorny 2014, Level II, n=223
PPV	Biopsy naïve, PI-RADS	0.92 (0.88-0.95)	0.93 (0.89-0.96)	⊕⊕⊕⊙	Pokorny 2014 Level II, n=223
NPV	Biopsy naïve, PI-RADS	0.97 (0.93-0.99)	0.72 (0.65-0.78)	⊕⊕⊕⊙	Pokorny 2014 Level II, n=223
CDR (RCT)	Prev. neg. biopsy, PI-RADS	27/104 (26%)	26/104 (25%)	⊕⊕⊕⊕	Arsov 2015 Level II, n=210
—	—	**MR-US fusion [95%CI]**	**TRUSGB [95%CI]**	—	—
Sensitivity	Biopsy naïve, PI-RADS	0.89 (0.80 – 0.94)	0.67 (0.56 – 0.76)	⊕⊕⊕⊕	Schoots 2015, Level III-2, n=1,657
Specificity	Biopsy naïve, PI-RADS	0.95 (0.75 – 1.00)	0.89 (0.69 – 0.97)	⊕⊕⊙⊙	Fiard 2013, Level III-3, n=30
PPV	Biopsy naïve (57%), PI-RADS	0.91	0.83	⊕⊕⊙⊙	Fiard 2013, Level III-3, n=30
NPV	Biopsy naïve, PI-RADS (57%)	0.95	0.94	⊕⊕⊙⊙	Fiard 2013, Level III-3, n=30
CDR (RCT)	Mixed patient pop, PI-RADS	26% to 38%	25% to 49%	⊕⊕⊕⊕	Arsov 2015, Level II; Baco 2016 Level II, total n = 385
CDR (meta-analysis)	Mixed patient pop, PI-RADS	36%	30%	⊕⊕⊕⊕	Wu 2015; Level III-2, n=2,481

[*] GRADE Working Group grades of evidence (Guyatt *et al*. 2013)
CI = confidence interval; MR = magnetic resonance; PI-RADS = Prostate Imaging-Reporting and data System; TRUSGB = transrectal ultrasound-guided biopsy; US = ultrasound
⊕⊕⊕⊕ **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.

A summary of the diagnostic accuracy of MR-US fusion for men under active surveillance is provided in Table 5. No studies were found that reported the relevant measures of diagnostic accuracy for MR-in gantry relative to systematic TRUSGB/TPUSGB.

Table 5 Summary of findings for the accuracy of MR-US fusion, relative to systematic TRUSGB, including patients classified as PI-RADS 4-5, with an assumed pre-test probability (prevalence) of intermediate/high-risk cancer at 89% (men under AS)

Outcomes	Participants	Intervention	Supportive comparator	Quality of evidence	Study, level of evidence, n
—	—	MR-US fusion [95%CI]	Systematic TRUSGB [95%CI]	—	—
Sensitivity	LR PCa, Epstein criteria	0.54 (0.41-0.68)	0.67 (0.56 – 0.76)	⊕⊕⊙⊙	Okoro 2015, Level III-1, n=50
Specificity	LR PCa, Epstein criteria	0.86 (0.74-0.93)	0.89 (0.69 – 0.97)	⊕⊕⊙⊙	Okoro 2015, Level III-1, n=50
PPV	LR PCa, Epstein criteria	0.83 (0.66-0.92)	0.78 (0.60-0.89)	⊕⊕⊙⊙	Okoro 2015 Level III-1, n=50
NPV	LR PCa, Epstein criteria	0.59 (0.41-0.75)	0.49 (0.32-0.66)	⊕⊕⊙⊙	Okoro 2015 Level III-1, n=50

* GRADE Working Group grades of evidence (Guyatt *et al.* 2013)
AS = active surveillance; CI = confidence interval; LR = low risk; MR = magnetic resonance; PI-RADS = Prostate Imaging-Reporting and data System; PCa = prostate cancer; TRUSGB = transrectal ultrasound-guided biopsy; US = ultrasound
⊕⊕⊕⊕ **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.

The main limitations of these results are associated with using 12-core systematic TRUSGB (without mpMRI guidance) as the reference standard, and that the PI-RADS scoring system was not used. Further, there was no data for estimates of diagnostic accuracy of MR-in gantry versus systematic TRUSGB/TPUSGB. The applicability of these results is discussed in Section C2.

MR-US fusion in men under active surveillance.

Racabal 2016 compared MR-US fusion plus cognitive TRUSGB plus systematic TRUSGB (group 1) with cognitive TRUSGB plus systematic TRUSGB (group 2) in men under active surveillance. The additional utility of including MR-US fusion in group 1 resulted in fewer missed intermediate/high-risk cancers compared with group 2 (6% vs. 9%, respectively). However, using MR-targeted biopsy alone (MR-US fusion + cognitive TRUSGB; group 3) resulted in more missed intermediate/high-risk cancer compared with group 2 (13% vs 9% respectively).

Clinical Claim

The proposed clinical claim for both MRI-guided biopsy procedures in the diagnosis of prostate cancer is:

- Both MR-in gantry and MR-US fusion offer superior clinical efficacy compared with:
  1) Cognitive TPUSGB (with mpMRI guidance); and
  2) Systematic TRUSGB/TPUSGB (without mpMRI guidance); and
- Both MR-in gantry and MR-US fusion offer superior safety compared with
  1) Cognitive TPUSGB (with mpMRI guidance); and
  2) Systematic TRUSGB/TPUSGB (without mpMRI guidance).

12. Economic evaluation

The application presented a cost-utility analysis. A summary of the key characteristics of the economic evaluation for model 1 (relative to cognitive TPUSGB) is summarised in Table 6.

Table 6 Summary of the economic evaluation for men suspected of PCa (model 1)

Perspective	Direct health system i.e. MBS, PBS
Comparators	1. Cognitive TPUSGB; main comparator (in main body) 2. Systematic TRUSGB (75%)/TPUSGB (25%); supportive comparator (in Attachment)
Type of economic evaluation	Cost-utility
Type of model	2 stage: 1) Decision tree for diagnostic accuracy of tests 2) Markov model for long-term effects of treatment and monitoring prostate cancer
Sources of evidence	• Meta-analysis of diagnostic accuracy studies (Wegelin 2016) • Clinical studies (Pokorny 2014) • Registry data
Starting age	65 years.
Time horizon	Lifetime (25 years)
Outcomes	QALYG, LYG, cost
Methods used to generate results	Cohort expected value analysis, Markov model
Health states	9-state Markov model
Cycle length	1 year
Discount rate	5%
Software packages used	TreeAge Pro 2015 R2

LYG = life years gained; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; QALYG = quality-adjusted life years gained; TRUSGB = transrectal ultrasound-guided biopsy; TPUSGB = transperineal ultrasound-guided biopsy

The overall costs and outcomes, and incremental costs and outcomes as calculated for the index test and comparator in the model, with the base case assumptions, are shown in Table 7 for model 1 base case (cost of TPUSGB at $925.72) and Table 8 for scenario analysis (cost of TPUSGB at $4,100).

Table 7 Cost-effectiveness results for population 1 (men suspected of PCa) [a]

	Cost	Incremental cost	Effectiveness (QALYs)	Incremental QALYs	ICER [b]
Cognitive TPUSGB	$30,957	—	8.10	—	
Intervention 1: MR-in gantry	$32,480	$1,523	8.11	0.01	$163,993
Intervention 2:MR-US fusion	$31,102	$145	8.11	~0.005	$31,011

ICER = Incremental Cost Effectiveness Ratio; MR = magnetic resonance; PCa = prostate cancer; US = ultrasound; QALY = quality-adjusted life year

[a] Cost of TPUSGB, applied to cognitive TPUSGB and MR-US fusion was estimated at $925.72

[b] Differences in ICER due to rounding from TreeAge Pro 2015

Table 8 Cost-effectiveness results for scenario analysis 1 (cost of TPUSGB at $4,100 [c]; applicant advised)

	Cost	Incremental cost	Effectiveness (QALYs)	Incremental QALYs	ICER [a]
Cognitive TPUSGB	$36,285	—	8.10	—	
Intervention 1: MR-in gantry	$35,337	-$948	8.11	0.01	Dominant [b]
Intervention 2:MR-US fusion	$36,213	-$72	8.11	~0.005	Dominant [b]

ICER = Incremental Cost Effectiveness Ratio; MR = magnetic resonance; PCa = prostate cancer; US = ultrasound; QALY = quality-adjusted life year
[a] Differences in ICER due to rounding from TreeAge Pro 2015
[b] Albeit marginal gain in QALYs

The model was sensitive to the cost of TPUSGB, the assumption of a disutility for biopsy, the assumption of disease upgrading for false negatives was high and favoured MR-US fusion and MR-in gantry; and the assumption of repeat biopsy was moderate and favoured MR-US fusion and MR-in gantry.

Other key areas of uncertainty were the prevalence of cancer in patients classified as PI-RADS 4-5 from baseline mpMRI, the assumption that the diagnostic accuracy of cognitive TPUSGB was similar to pooled results for cognitive TPUSGB/TRUSGB, and the limited data on the diagnostic accuracy of MR-guided biopsy procedures in men under active surveillance.

13. Financial/budgetary impacts

A market-based approach was used to estimate the financial implications of the introduction of MR-in gantry and MR-US fusion on the MBS. This approach used the number of biopsy services performed in the period 2013-15. From this, a change (growth) rate of -10.9% was estimated and applied over the next five years.

The financial implications to the MBS resulting from the proposed listing of MR-in gantry and MR-US fusion are summarised in Table 9.

Table 9 Total costs to the MBS associated with MR-in gantry and MR-US fusion and subsequent treatments

	Year 1	Year 2	Year 3	Year 4	Year 5
Expected number of biopsies	14,248	12,694	11,309	10,076	8,977
Estimated use	—	—	—	—	—
MR-in gantry (10% uptake)	1,425	1,269	1,131	1,008	898
MR- US fusion (90% uptake)	12,824	11,425	10,179	9,068	8,079
Estimated MBS costs	—	—	—	—	—
MR-in gantry	$2,785,565	$2,481,710	$2,211,000	$1,969,820	$1,754,948
MR-US fusion	$4,251,015	$3,787,306	$3,374,178	$3,006,116	$2,678,203
Co-administered services [a]	$3,977,232	$3,543,387	$3,156,867	$2,812,510	$2,505,715
Additional treatments [b]	$2,731,291	$2,433,356	$2,167,921	$1,931,439	$1,720,754
Total cost offsets [c]	-$9,142,496	-$8,145,214	-$7,256,717	-$6,465,140	-$5,759,909
Net MBS costs	**$4,602,607**	**$4,100,545**	**$3,653,249**	**$3,254,745**	**$2,899,711**

MBS = Medicare Benefits Schedule; MR = magnetic resonance; RP = radical prostatectomy; TPUSGB = transperineal ultrasound-guided biopsy; TRUSGB = transrectal ultrasound-guided biopsy; US = ultrasound
[a] Includes MBS costs of prostate ultrasound (56507), examination of biopsy specimen (72825), and general anaesthesia for TPUSGB (17615; 23051)
[b] Due to the change in a positive test (based on the prevalence and sensitivity and specificity of each biopsy modality). Patients with intermediate/high-risk cancer received RP or radiation therapy/hormone therapy combination, and patients with low/intermediate-risk would remain in active surveillance
[c] Decrease in TRUSGB (75%) and TPUSGB (25%) if MR-in gantry or MR-US fusion was listed

By listing MR-in gantry and MR-US fusion, the MBS would incur costs of approximately $18.5 million over the next five years.

14. Key issues from ESC for MSAC

ESC noted that this application proposes the listing of two magnetic resonance imaging MRI-guided biopsy procedures for diagnosis of prostate cancer in the MBS:

- MR-in gantry: performed within the bore (gantry) of the magnet requiring MR-compatible equipment. A transrectal approach is typically used with local anaesthesia.
- MR-US fusion: performed either with transrectal ultrasound guided biopsy (TRUSGB) or transperineal ultrasound guided biopsy (TPUSGB) using software fusion of previously acquired multiparametric MRI (mpMRI) images with ultrasound images.

ESC noted that two patient populations have been identified for both MRI-based biopsy procedures:

- Population 1: men who are suspected of having prostate cancer on the basis of a Prostate Imaging-Reporting and Data System (PI-RADS) 4–5 lesion on diagnostic mpMRI; and
- Population 2: men undergoing active surveillance for prostate cancer who develop a PI-RADS 4–5 lesion on diagnostic mpMRI.

ESC noted that cognitive TPUSGB, involving a review of previously taken mpMRI images and real-time ultrasound guidance (without fusion), was updated as the main comparator based upon advice from the applicant that this approach is now established in clinical practice in Australia. ESC noted that systematic TRUSGB/TPUSGB is still performed and is nominated as a supportive comparator.

ESC deliberated as to whether cognitive TPUSGB or systematic TRUSGB/TPUSGB should be accepted as the appropriate main comparator. ESC considered that more information comparing these two procedures was required to assist in resolving this issue.

ESC noted that no direct comparative evidence on safety of MR-in gantry or MR-US fusion versus cognitive TPUSGB or systematic TRUSGB/TPUSGB was identified. The evaluation of safety was instead based on evidence for TRUSGB and TPUSGB. ESC noted that the adverse events observed primarily relate to the method of approach (i.e. whether transrectal or transperineal) and observed that MR-in gantry and MR-US fusion use the same delivery approaches.

ESC noted that no direct comparative evidence on effectiveness of MR-in gantry or MR-US fusion versus the nominated comparators was identified and therefore a linked evidence approach was used.

For population 1 both MR-in gantry and MR-US fusion were considered by ESC to be at least similar in diagnostic accuracy to cognitive TPUSGB with higher sensitivity. ESC noted that there was limited evidence for men under active surveillance for cognitive TPSUGB. ESC considered that both MR-in gantry and MR-US fusion outperform systematic TRUSGB/TPUSGB in terms of diagnostic accuracy with a significantly higher sensitivity but similar specificity in population 1. ESC noted that, while evidence was not available for MR-in gantry, MR-US fusion appears to outperform systematic TRUSGB/TPUSGB with significantly higher sensitivity but similar specificity in population 2.

ESC noted data indicating higher reclassification rates in men undergoing active surveillance for prostate cancer using MR-in gantry and MR-US fusion compared with standard

TRUSGB. ESC noted that the evidence for the impact of delayed treatment in men with a false negative result was mixed.

ESC considered that based on the limited evidence available MR-in gantry or MR-US fusion appear to have at least non-inferior safety and superior effectiveness.

ESC noted that an economic model comparing MR-in gantry and MR-US fusion with cognitive TPUSGB was included in the application for population 1 (model 1) but not for population 2. ESC also noted that economic models for populations 1 (model 2) and population 2 (model 3) in which systematic TRUSGB/TPUSGB is the comparator were included as an attachment.

ESC considered the application of diagnostic accuracy results and the use of Australian data where possible in the three economic models to be appropriate. ESC noted that the use of the same disutility across all biopsy techniques was conservative due to variation in the number of biopsy needles used across procedures. However, ESC noted that disutility is varied in the sensitivity analysis. ESC questioned why Table 101 specifies 25 years for model 1 when 30 years is specified in the duration of the economic model.

The ICERs for MR-in gantry and MR-US fusion compared to cognitive TPUSGB for population 1 were $163,993 per QALY and $31,011 per QALY respectively. ESC noted that in their pre-ESC response the applicant advised that the cost of cognitive TPUSGB (~$926) used in this model was below current cost for this procedure. The applicant requested that the cost of all MR-guided biopsy procedures reflect the current market price (MR-in gantry $2,600, MR-US fusion $4,100, cognitive TPUSGB $4,100). ESC noted that the base case for model 1 was revised using these fees in the rejoinder resulting in MR-in gantry and MR-US dominating cognitive TPUSGB.

ESC was concerned that the cost effectiveness of MR-in gantry and MR-US relies heavily on the assumed cost of the comparator. ESC agreed that the initial cost for cognitive TPUSGB (~$926) was low but questioned the validity of using estimated current market prices in the economic model. ESC noted that setting a cost for cognitive TPUSGB was difficult as there is no MBS item for this procedure.

ESC noted the ICERs from model 2 and model 3 in which MR-in gantry and MR-US fusion were compared with systematic TRUSGB/TPUSGB. For population 1 the ICERs for MR-in gantry and MR-US fusion were $56,267 per QALY and $5,000 per QALY respectively. For population 2 the ICER for MR-in gantry was $47,985 per QALY and for MR-US fusion it was $1,474 per QALY.

ESC noted that the listing of MR-in gantry and MR-US fusion in the MBS was associated with additional costs in the initial base case financial estimates and cost savings in the rejoinder estimates.

ESC noted that an uptake rate of 10% was used for MR-in gantry in the financial estimates. ESC considered that the uptake rate was difficult to estimate but could increase over time.

ESC noted that in their pre-ESC response the applicant indicated they were not seeking a new MBS item for MR-US fusion. ESC also noted that the applicant had requested a pathologist fee ($300) be added to the proposed MBS item for MR-in gantry cost and questioned the need for such an addition.

ESC noted that under current regulations urologists would not be classified as eligible to perform an MRI and hence would not be able to claim the MR-in gantry item. ESC advised that consideration be given to splitting the MBS fee between radiologists and urologists. From a consumer perspective, ESC noted that widespread adoption had occurred despite lack of reimbursement which raises equity of access issues. The consumer wants to know who benefits (provider compared with consumer) and by how much. The consumer also noted that it was clear whether the widespread practice despite the lack of reimbursement reflected referrals or consumer preference and/or need.

From a consumer perspective, ESC noted that mpMRI was likely to be more acceptable to patients than biopsy and that some consumers were already paying for the procedure privately. ESC noted that there is potential for mpMRI to be used to reassure clinicians and men that they do not have significant PCa rather than for diagnostic purposes.

15. Other significant factors

Nil.

16. Applicant's comments on MSAC's Public Summary Document

Australian men with financial resources are undergoing targeted biopsies of the prostate in increasing numbers, and those without resources are still undergoing blind TRUS biopsy of the prostate. Australian men should have equity of access to state of the art diagnostic imaging in prostate cancer. Targeted prostate biopsy is integral to the image based diagnostic pathway. When the comparator for a targeted biopsy is a blind TRUS biopsy, targeted biopsy is far better both in diagnostic accuracy and assessment of grade and requires fewer cores to confirm the radiological diagnosis. Targeted biopsy is now used widely throughout the world. Historically, MRGB ("in-bore") was the targeting technique used to validate PIRADS and to do the early validating prospective trials of the diagnostic pathway both internationally and in Australia. Currently, the infrastructure required for MRGB is restricted to very few radiology units around the country. MRGB does not incur costs of anaesthesia and day-case hospitalization. Currently, the patients that would benefit from MRGB are being penalized financially. In light of this application being rejected by MSAC we propose that MSAC considers allowing these patients to get the same rebate as patients get for other forms of targeted biopsy using ultrasound, by altering the descriptor of Item 37219 to "using ultrasound or MRI". This approach would be revenue neutral. While it would involve another MRI, it would not require the current ultrasound item number, and, in addition, MRGB would avoid associated health costs of anaesthesia and hospitalization which are currently reimbursed with Ultrasound targeting techniques.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website:
visit the MSAC website