MSAC Application 1794

Irreversible Electroporation (IRE) for prostate tumour tissue in patients with prostate cancer

Applicant: GETZ HEALTHCARE Pty Ltd

PICO Confirmation

Summary of PICO criteria to define question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

Table 1 PICO for IRE in patients with intermediate-grade or high-risk features, low-grade localised unifocal prostate tumours: PICO Set 1

Component	Description
Population	Patients with localised unifocal prostate tumours, evident on imaging, characterised as: • intermediate-grade, ISUP 2 or 3 (Gleason score 7 [3+4 or 4+3]) or • low-grade, ISUP 1 (Gleason 6 [3+3]), with high-risk features, not clinically appropriate for active surveillance with life expectancy >10 years at the time of diagnosis, no contraindication to general anaesthesia, and no pacemaker dependency
Prior tests	High-quality transperineal targeted and mapping biopsies; MRI or PSMA-PET scan if patients unable to undergo MRI
Intervention	IRE
Comparators	Radical prostatectomy Radiation therapy including radiotherapy and brachytherapy
Outcomes	Safety • Erectile function – maintenance of potency • Genitourinary AEs (e.g. urinary incontinence, urinary retention, bowel dysfunction, fistula) • Treatment-related AEs measured using either: o Clavien-Dindo classification for surgically treated patients (grade ≥3) o CTCAE classification for non-surgically treated patients (grade ≥3) Clinical effectiveness • Overall survival • Cancer-specific survival • Metastasis-free survival • Treatment failure (histopathology assessment, MRI) • Rate of negative in-field biopsy • Rates of in-field or out-of-field recurrences • Need for secondary (i.e. salvage treatment rate) or adjuvant treatment • Recovery time • PSA levels • Patient-reported health status (EPIC, IPSS-QoL, IIEF-15, EQ-5D, SHIM) • Patient satisfaction

Component	Description
	Non-health outcomes • Economic and social: workplace productivity and absenteeism, preservation of patient involvement in family and community life with minimal interference, caregiving load and wellbeing • Ethical and organisational: accessibility of IRE and equity for regional patients Healthcare resource use • Operating time • Length of hospital stay • Costs associated with the intervention and comparators, including cost of post-cancer lesion assessments (e.g. biopsies, specialist appointments, MRI, PSA testing) • Cost effectiveness • Budget impact
Assessment question	What is the safety, effectiveness and cost-effectiveness of IRE compared to radical prostatectomy or radiation therapy in intermediate-grade or, low-grade with high-risk features localised unifocal prostate cancer patients (ISUP 2 or 3 [Gleason score 7] or ISUP1 [Gleason score 6], respectively)?

AE = adverse event; EPIC = Expanded Prostate Cancer Index Composite; EQ-5D = EuroQol 5-dimension questionnaire; IIEF-15 = International Index of Erectile Function 15-item questionnaire; IPSS-QoL = international prostate symptom score – quality of life; IRE = irreversible electroporation; ISUP = International Society of Urological Pathology; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; PSMA-PET = prostate-specific membrane antigen positron emission tomography; SHIM = sexual health inventory for men

The population defined in the PICO set as low-to-intermediate-grade prostate cancer patients (Gleason score = 7 [3+4 or 4+3]) has been amended to intermediate-grade prostate cancer patients to align with the grading system.

Table 2 PICO for IRE in patients with localised relapsed prostate cancer after radiation therapy: PICO Set 2

Component	Description
Population	Patients with localised unifocal recurrent prostate cancer after radiation therapy, with life expectancy ≥5 years, no contraindication to general anaesthesia, and no pacemaker dependency
Prior tests	High-quality transperineal targeted and mapping biopsies; MRI or PMSA-PET scans
Intervention	IRE
Comparators	Radical prostatectomy Radiation therapy including radiotherapy and brachytherapy

Outcomes	Safety
	• Erectile function – maintenance of potency
	• Genitourinary AEs (e.g. urinary incontinence and retention, bowel dysfunction, fistula)
	• Treatment-related AEs measured using either:
	  ○ Clavien-Dindo classification for surgically treated patients (grade ≥3)
	  ○ CTCAE classification for non-surgically treated patients (grade ≥3)

Component	Description
	Clinical effectiveness • Overall survival • Cancer-specific survival • Metastasis-free survival • Treatment failure (histopathology assessment, MRI) • Rate of negative in-field biopsy • Rates of in-field or out-of-field recurrences • Recovery time • PSA levels • Need for adjuvant treatment • Patient-reported health status (EPIC, IPSS-QoL, IIEF-15, EQ-5D, SHIM) • Patient satisfaction Non-health outcomes • Economic and social: workplace productivity and absenteeism, preservation of patient involvement in family and community life with minimal interference, caregiving load and wellbeing • Ethical and organisational: accessibility of IRE and equity for regional patients Healthcare resource use • Operating time • Length of hospital stay • Costs associated with the intervention and comparators, including cost of post-cancer lesion assessments (e.g. biopsies, specialist appointments, MRI, PSA testing) • Cost of cancer relapse and secondary treatment • Cost effectiveness • Budget impact
Assessment question	What is the safety, effectiveness and cost-effectiveness of IRE compared to radical prostatectomy or radiation therapy in patients with localised recurrent prostate cancer after radiation therapy?

AE = adverse event; EPIC = Expanded Prostate Cancer Index Composite; EQ-5D = EuroQol 5-dimension questionnaire; IIEF-15 = International Index of Erectile Function 15-item questionnaire; IPSS-QoL = international prostate symptom score – quality of life; IRE = irreversible electroporation; ISUP = International Society of Urological Pathology; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; PSMA-PET = prostate-specific membrane antigen positron emission tomography; SHIM = sexual health inventory for men

Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of irreversible electroporation (IRE) for prostate tumour tissue was received from Getz Healthcare Pty Ltd by the Department of Health and Aged Care.

The application claims that:

1) use of IRE results in superior safety and non-inferior effectiveness compared to radical prostatectomy (RP) and radiation therapy (RT) in the primary treatment of intermediate-grade or low-grade unifocal localised prostate tumour tissue with high-risk features,
2) use of IRE results in superior safety and non-inferior effectiveness compared to RP and RT as a salvage treatment for patients with localised unifocal recurrent prostate cancer after RT.

The application claims IRE has a faster recovery time, a lower incidence of genitourinary adverse events (AEs) and reduced treatment-related morbidity. The application also claims that IRE is non-inferior to its comparators with regards to oncological outcomes.

The intervention is approved by the Therapeutic Goods Administration (TGA), under the following listings:

- ARTG ID 205431 – Electrode, electrosurgical, active, foot-controlled, single use
- ARTG ID 205432 – Electrosurgical system generator, general-purpose

These products are not registered in the Prescribed List of Medical Devices and Human Tissue Products. However, the applicant indicated intent for a future application for funding of the electrodes under the Prescribed List.

PICO criteria

Population

Two PICO sets were developed, reflecting the different stages of the treatment pathway in which the proposed intervention would be used. Each PICO set addresses a unique patient population, with different clinical characteristics and disease stages. Additionally, notable differences exist in the morbidity associated with the comparators at each stage of treatment (personal communication, applicant's expert, pre-PASC meeting, 18 February 2025) (Valle et al. 2021). The proposed population includes patients with localised primary or recurrent prostate cancer whose index tumour is unifocal.

Disease definition

The prostate is a small, walnut-sized gland of the male reproductive system—located anterior to the rectum and encircling part of the urethra—whose primary function is to produce seminal fluid (Cancer Council 2022). As men age, the prostate naturally enlarges, which can lead to urinary difficulties called benign prostatic hyperplasia. This is not necessarily a sign of cancer. Prostate cancer develops when abnormal cells in the prostate grow uncontrollably, with the majority of cases being adenocarcinomas (Cancer Australia 2024). These cancers originate from the glandular cells lining the prostate's acini, which are responsible for secreting prostate fluid. Most cases are classified as localised prostate cancer, meaning the disease remains confined to the prostate gland without spreading to lymph nodes or distant organs.

This form is typically slow-growing and asymptomatic. Symptoms (not specific to prostate cancer) may appear at a more advanced stage, including urinary difficulties, pain and/or blood in the urine or semen, back pain, leg weakness, unexplained weight loss, fatigue, shortness of breath, dizziness or pale skin (Cancer Australia 2024).

Disease burden

Prostate cancer is the most frequently diagnosed cancer among Australian men. The Australian Institute of Health and Welfare (AIHW) estimates that 26,368 men will have been diagnosed with the disease in 2024, accounting for 28% of the cancers diagnosed in males for the year (AIHW 2024). The age-standardised incidence rate is projected to be 204.4 per 100,000 men (97.1 per 100,000 people). In males aged 65–69 years, an estimated 5,579 cases of prostate cancer were expected to be diagnosed in 2024, corresponding to an age-specific incidence rate of 850.6 cases per 100,000 males.

Prostate cancer is also the second leading cause of cancer-related deaths among Australian men, behind lung cancer (Prostate Cancer Foundation of Australia 2024). In 2024, prostate cancer was expected to cause approximately 3,900 deaths, equating to an age-standardised mortality rate of 29.0 per 100,000 men (14.4 per 100,000 people) (AIHW 2024).

The overall 5-year relative survival rate for prostate cancer, reflecting the probability of being alive 5 years post-diagnosis compared to the general population, was 95.8% (95% CI: 95.5–96.0%) for patients diagnosed between 2016 and 2020 (AIHW 2024). This rate was nearly 100% for patients with stage I–III disease, whereas it was significantly lower (36%) for those with stage IV disease (National Cancer Control Indicators 2019).

According to the Australia and New Zealand prostate cancer registry, among 80,904 men with available National Comprehensive Cancer Network (NCCN) risk classification data from 2015 to 2021, 19% were classified as low risk, while 44% were classified as intermediate risk of developing prostate cancer (Cancer Council Victoria 2024; Ong, WL et al. 2024).

The incidence of recurrence after radiotherapy varies depending on the definition used, with biochemical recurrence—defined as a rising prostate-specific antigen (PSA) level, indicating potential cancer recurrence—reported in 15–57% of cases (Adams et al. 2023). Confirmed local failure requiring salvage therapy occurs in approximately 3–10% of patients (Valle et al. 2021). In the Valle et al. (2021) meta-analysis, local failure was identified by biopsy, imaging, physical examination, or biochemical recurrence criteria. Local salvage options included RP, brachytherapy, cryotherapy, high-intensity focused ultrasound (HIFU) and stereotactic body radiotherapy (SBRT).

Stage and grade terminology

Prostate cancer is characterised by its stage (anatomical extent of the disease) and grade (histological aggressiveness of the tumour). These 2 parameters are fundamental in guiding treatment and predicting outcome.

Stage

Stage refers to the extent of prostate cancer spread within the body. The most commonly used staging system is the tumour–node–metastasis (TNM) classification, which assesses the size and extent of the primary tumour (T), the involvement of regional lymph nodes (N), and the presence or absence of distant

metastases (M) (Cornford 2024). This system provides a standardised framework for determining disease progression and guiding treatment decisions (Table 3).

Table 3 Clinical TNM classification of prostate cancer

T – Primary Tumour (stage based on digital rectal examination only)
TX Primary tumour cannot be assessed T0 No evidence of primary tumour T1 Clinically inapparent tumour that is not palpable T1a Tumour incidental histological finding in ≤5% of tissue resected T1b Tumour incidental histological finding in >5% of tissue resected T1c Tumour identified by needle biopsy (e.g. because of elevated prostate-specific antigen) T2 Tumour that is palpable and confined within the prostate T2a Tumour involves half of one lobe or less T2b Tumour involves more than half of one lobe, but not both lobes T2c Tumour involves both lobes T3 Tumour extends palpably through the prostatic capsule T3a Extracapsular extension (unilateral or bilateral) T3b Tumour invades seminal vesicle(s) T4 Tumour is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles and/or pelvic wall
N – Regional (pelvic) Lymph Nodes[a]
NX Regional lymph nodes cannot be assessed N0 No regional lymph node metastasis N1 Regional lymph node metastasis
M – Distant Metastasis[b]
M0 No distant metastasis M1 Distant metastasis M1a Non-regional lymph node(s) M1b Bone(s) M1c Other site(s)

M = distant metastases; N = regional lymph nodes; T = primary tumour

[a] Metastasis ≤0.2 cm can be designated pNmi.

[b] When more than one site of metastasis is present, the most advanced category ((p)M1c) is used.

Prostate cancer stage I and stage II correspond to a tumour confined within the prostate (T1–T2, N0, M0), also called localised cancer.

Grade

The Gleason scoring system and the International Society of Urological Pathology (ISUP) Grade Group system are both used to assess the aggressiveness of prostate cancer, based on microscopic examination of tumour architecture (Table 4) (Cornford 2024). The Gleason score is determined by adding the most predominant cell pattern and the second-most common cell pattern of tumour growth seen in the prostate biopsy tissue, resulting in scores ranging from 6 (3+3) to 10 (5+5). If only one pattern is present, it is doubled, and in cases where three patterns exist, the most common and highest grades are used. Recognising the need for a more intuitive classification of risk stratification, the ISUP introduced the Grade Group system in 2014, which restructured the Gleason scores into five distinct groups. This system ranges from Grade Group 1 (Gleason 6, least aggressive) to Grade Group 5 (Gleason 9–10, most aggressive),

providing clearer prognostic information. Higher Grade Groups correlate with increased risk of progression, metastasis and mortality.

Table 4 Gleason score and ISUP 2019 grade system

ISUP Grade Group	Gleason Score	Interpretation
1	≤6	Low grade (well-differentiated)
2	7 [3+4]	Intermediate grade (mostly pattern 3 with some 4)
3	7 [4+3]	Intermediate grade (mostly pattern 4)
4	8	High grade (4+4, 3+5 or 5+3)
5	9–10	Highest grade (4+5, 5+4 or 5+5)

ISUP = International Society of Urological Pathology

Risk stratification

Optimal management of prostate cancer requires a comprehensive risk assessment, which includes—at a minimum—clinical stage, grade and PSA level (Mohler et al. 2019; Mottet et al. 2021). The European Association of Urology (EAU) guidelines acknowledge the impact of advanced imaging techniques such as magnetic resonance imaging (MRI), targeted biopsy and prostate-specific membrane antigen positron emission tomography/computed tomography (PSMA PET/CT) scan on risk stratification and treatment decisions, whereas the NCCN guidelines emphasise that these imaging modalities are not yet considered essential for staging.

The EAU and NCCN guidelines differ in their risk stratification of patients with localised intermediate-risk prostate cancer, particularly for T2c tumours (Mohler et al. 2019; Mottet et al. 2021). According to the EAU guidelines, patients with T2c disease are classified as high risk, while NCCN guidelines categorise them as intermediate risk. This distinction may influence treatment recommendations and prognostic expectations.

Risk stratification for patients with clinically localised intermediate-risk prostate cancer depends on the presence of at least one of the following criteria: PSA levels 10–20 ng/mL, Gleason score of 7 or ISUP grade group 2 or 3, or clinical stage T2b/T2c (depending on guideline). The low-risk group includes patients with PSA levels ≤10 ng/mL, Gleason score ≤6 or ISUP 1, and clinical stage T1–T2a.

There is no established risk stratification for radio-recurrent patients. Management is guided by a personalised assessment based on prognostic factors including PSA levels, PSA doubling time, tumour grade and imaging findings, particularly PSMA PET/CT scans to exclude metastatic disease.

Proposed population

PICO Set 1: patients with localised and unifocal primary prostate cancer

Patients with intermediate-grade prostate cancer with histologically confirmed ISUP score 2 or 3 (Gleason score 7 [3+4 or 4+3]) are defined as the primary target population for IRE (Rodriguez-Sanchez et al. 2025; Rokan & Reddy 2025).

Another group of patients likely to benefit from IRE was also described within the application, consisting of patients with histologically confirmed low-grade prostate cancer (ISUP 1, Gleason score 6 [3+3]) with high-risk features indicating a higher likelihood of cancer progression. According to the applicant's experts and guidelines (Cornford 2024; Eastham et al. 2022; Mottet et al. 2021), this very small group of patients is not clinically appropriate for active surveillance (the standard of care [SoC] for this staging); whole gland

therapy would be recommended due to the nature of the tumour tissue. Currently, according to the applicant's experts, there is no clear consensus in the guidelines nor recommendations for identifying these high-risk features in low-grade patients (personal communication, pre-PASC meeting, 18 February 2025). According to the applicant's experts and the literature (Ong, S et al. 2023), several factors should be taken into account before offering IRE as an option for these patients, including a large-volume tumour, abnormality visible on MRI (Cornford 2024; Rodriguez-Sanchez et al. 2025), and a strong family history of prostate, ovarian or breast cancer (Cornford 2024). The applicant's experts also highlighted that these patients tend to be younger than other prostate cancer patients and may exhibit concerning characteristics such as a high PSA velocity, abnormal PSA density or radiological findings discordant with biopsy results. To define this subgroup, the applicant's experts suggested the following criteria: prostate imaging reporting and data system (PIRADS) 4–5 lesions, high PSA density (>0.15) or an elevated maximum standardised uptake value (SUV max) on PET scan (e.g. >6). This subpopulation should be treated on a case-by-case basis, taking into account the patient's choice and the opinion of a multidisciplinary team variously composed of urologists, medical oncologists, radiation oncologists, oncology nurses, behavioural practitioners and others including fellow patients (Cornford 2024).

Patient selection criteria for the use of focal therapy for those with low-risk prostate cancer vary between consensus statements (Ong, S et al. 2023). Three of 6 consensus statements address these criteria as follows:

- It is acceptable not to treat Gleason score 6 if the maximum core length is up to 5 mm
- Gleason score 6 with 1 mm in one core is acceptable in untreated area
- Patients with unilateral localised low-risk prostate cancer can be offered focal therapy if both standard therapy and active surveillance are declined and the following requirements are met: Gleason score 6, PSA <10 ng/mL, normal digital rectal exam, and maximum 50% positive biopsy cores of one lobe only in systematic biopsy diagnosis by multi-parametric MRI (mpMRI), fusion biopsy and systematic biopsy.

Ong et al. (2023) stated that this patient subpopulation could be defined as 'high-volume' Gleason 6 disease, noting that advanced imaging such as PSMA PET/CT could help refine the parameters (Ong, S et al. 2023). The authors also emphasised that active surveillance remains a viable option until significant disease is detected, underscoring the need for further clarification on the role of focal therapy in this subgroup.

Experts explained during the pre-PASC meeting that if a second foci was adjacent to the targeted tumour and could be treated within the same single ablation field, the tumour could be treated with IRE. The lesion must be a unifocal index tumour, and treatment should only be considered if low-risk cancer is found outside the index lesion, while the remainder of the prostate can be effectively managed through active surveillance.

PICO Set 2: patients with localised and unifocal recurrent prostate cancer after radiation therapy

Recurrence of prostate cancer following radiotherapy is common, usually presenting as metastatic disease. The application suggests that patients with unifocal localised recurrence of intermediate-risk prostate cancer may benefit from focal therapy (MSAC Application 1794, PICO Set, p1) (Geboers et al. 2023; Gielchinsky & Lev-Cohain 2023). Yaxley et al. (2022) reported that patients with high-grade prostate cancer after salvage IRE had a low risk of in-field recurrence on biopsy (0 of 7 patients) (Yaxley et al. 2022).

Local recurrence of clinically significant disease after radiotherapy is estimated to occur in 20% of patients, forming a subgroup that is challenging to treat due to the limited treatment options available, and the high rate of genitourinary and gastrointestinal toxicities associated with salvage therapies (Geboers et al. 2023). This approach aims to minimise morbidity associated with retreatment using whole-gland therapy, which further burdens patients who have already experienced significant morbidity from their initial treatment, while limiting cancer progression (Cornford 2024; Valle et al. 2021). Management of isolated local failure after definitive radiotherapy remains controversial (as described below in Management of localised prostate cancer patients), with limited consensus recommendations available (Valle et al. 2021).

Further eligibility requirements for PICO Set 1 and 2 populations

Patients eligible for inclusion in this proposed population must have a tumour confined to the prostate (localised), life expectancy >10 years for primary prostate cancer or ≥5 years for recurrence (Schaeffer et al. 2024), no contraindication to general anaesthesia and no pacemaker dependency. The tumour must be thoroughly evaluated using high-quality transperineal targeted and mapping biopsies, and must be clearly visible on imaging. Proceeding with the IRE procedure requires precise cross-referencing between imaging and tissue biopsy.

The proposed populations for PICO Sets 1 and 2 correspond to the patient characteristics selected for focal therapy in the consensus statements (Ong, S et al. 2023).

Management of localised prostate cancer patients

This section is covered in detail in Clinical management algorithms.

In Australia, prostate cancer is typically identified in men aged 55–75 via PSA testing or prostate examinations conducted by primary care clinicians (MSAC Application 1794, PICO Set, p.1). If an elevated or abnormal PSA result is detected, the patient is referred to a specialist urologist for further evaluation. This assessment may include mpMRI or, for patients unable to undergo MRI for medical reasons, a PSMA PET/CT scan. If an abnormality is observed on imaging, a transperineal prostate biopsy is performed to confirm the presence of cancer and assess its grade (Light et al. 2024; Ong, S et al. 2023; Schaeffer et al. 2024). Once a diagnosis is confirmed, cases may be reviewed by a multidisciplinary team to develop an individualised treatment plan based on disease risk stratification and patient life expectancy and preferences. In private settings, a multidisciplinary team review is not always utilised with a low-grade diagnosis.

For localised prostate cancer, management options include active surveillance, RP, external beam radiotherapy (EBRT), brachytherapy and focal therapies including but not limited to HIFU, laser ablation or cryotherapy (Prostate Cancer Foundation of Australia 2023). The choice of treatment is influenced by tumour aggressiveness, patient comorbidity and the potential to preserve genitourinary and sexual function.

Management of locally recurrent prostate cancer after definitive radiotherapy remains controversial, largely due to the significant genitourinary and gastrointestinal toxicities associated with local salvage treatments (Valle et al. 2021). Unlike the approach to biochemical recurrence following RP, optimal management after radiotherapy remains unclear, primarily due to the absence of large prospective trials in this area. For patients with biochemical recurrence after primary RT, PSA monitoring is essential. A rise in PSA levels of 2 ng/mL above the post-radiotherapy nadir should trigger further imaging and biopsy to

confirm the recurrence. In cases of localised radio-recurrent prostate cancer, treatment options such as salvage prostatectomy, salvage radiotherapy or focal salvage therapies may be considered (Comparator(s) and Clinical management algorithms).

Estimated size of the eligible population

The application estimated that approximately 40% of newly diagnosed prostate cancer cases in 2022 were classified as intermediate risk, ISUP 2 and 3 (MSAC Application 1794, Application Summary, p.8) (Cancer Council Victoria 2024; Ong, WL et al. 2024). Based on the projected incidence of prostate cancer in 2024 (n = 26,386), it was estimated that 10,554 patients who have intermediate-risk prostate cancer may be suitable for IRE (AIHW 2024). The application also included a subgroup of patients with a high risk of cancer progression but classified as primary localised unifocal low-grade prostate cancer (ISUP 1, Gleason score 6) (MSAC Application 1794, PICO Set, p.1). The applicant's expert estimated this subgroup to be small (personal communication, pre-PASC meeting, 18 February 2025) (8Population 1: patients with localised and unifocal primary prostate cancer). According to additional data from the Prostate Cancer Outcomes Registry – ANZ, approximately 19% of Australian men are diagnosed with Gleason 6 prostate cancer, with around 15% of these low-grade cases proceeding to definitive treatment (Ong, WL et al. 2024). This represents approximately 2.9% of all prostate cancer patients. The applicant's experts stated that the number of patients requiring salvage treatment after RT is limited, as post-radiation failures are typically multifocal rather than unifocal. A small proportion of patients would benefit from salvage IRE, with one of the experts estimating he has performed 40 to 50 cases in his career (personal communication, pre-PASC meeting, 18 February 2025).

The application estimated that the IRE procedure would be used by 5% of the eligible population in the first year, corresponding to around 530 patients with primary or recurrent localised unifocal prostate cancer. The adoption rate is expected to rise gradually, reaching 20% by the fourth year.

PASC discussed the inclusion of the subgroup of prostate cancer patients with low-grade high-risk features and the need for a clearer definition of this subgroup. While guidelines recommend active surveillance for low-grade patients, there is a lack of consensus and explicit guidance on the identification of high-risk features for which active surveillance is not appropriate. The applicant's clinical experts indicated that this subgroup is a small proportion of the Gleason 6 population with tumours visible on MRI, where there is uncertainty about the biopsy result. The clinical experts noted that patients with high-risk features and a Gleason 6 biopsy are often misclassified and typically require an early repeat biopsy—if a tumour is visible on MRI, it generally indicates a higher grade than Gleason 6.

PASC considered that the main population for treatment was intermediate grade prostate cancer and recurrent prostate cancer after RT. PASC noted that if patients with low-grade (Gleason 6) cancer with high-risk features were included, the assessment would need to include evidence to demonstrate the benefit of IRE in this group.

PASC advised that it should be specified for the PICO Set 1 population that disease must be evident on imaging. This is based on advice from the applicant's clinical experts that disease must be visible on MRI (or an MRI surrogate such as PSMA PET).

Intervention

IRE is a minimally invasive, nonthermal ablation procedure designed to selectively destroy cancerous tissue, while preserving adjacent healthy structures (Blazevski, A. et al. 2020; Jourabchi et al. 2014). The focal therapy is performed using the NanoKnife System (AngioDynamics, Inc.), which delivers short pulses

of high-voltage direct current through inserted electrodes, creating irreversible nanopores in the cell membranes of targeted tissue. Unlike heat-based ablation methods, this disruption of cellular homeostasis leads to a process of natural cell death with minimal damage to surrounding vessels, nerves and connective tissue, leaving sharp, well-defined ablation zone margins (Faiella et al. 2024; Liu et al. 2024). These characteristics are designed to reduce morbidity by preserving genitourinary and sexual function, while ensuring adequate cancer control (MSAC application 1794, PICO Set, p.2 and 4).

IRE is a therapeutic technology that can be applied regardless of tumour location within the prostate. IRE would replace RP and RT for patients with localised intermediate-grade or high-risk features, low-grade prostate cancer (Population). The applicant's experts suggested that patients may undergo IRE twice in their lifetime (personal communication, pre-PASC meeting, 18 February 2025) (Rodríguez-Sánchez et al. 2024). IRE is also proposed as a salvage treatment for patients with localised intermediate-grade prostate cancer that has recurred after RT. IRE would provide an additional treatment option for this population.

The NanoKnife System for soft tissue ablation is currently the only device approved by the TGA. It requires:

- an electrosurgical system generator (Australian register of therapeutic goods (ARTG) 205432)
- single-use monopolar electrodes (ARTG 205431)

The proposed health technology is currently not funded in Australia for the same or another clinical indication.

Other potential devices, including high-frequency irreversible electroporation (H-FIRE), may be considered potential near-market comparators rather than fully established options (Wang, H; 2022; Wang, H; 2024). H-FIRE, an advanced form of IRE, uses very short, high-frequency bipolar pulses, which appear to result in more uniform ablation, reduced muscle contractions and lower operator dependency (He et al. 2021; Rolong, Schmelz & Davalos 2017; Siddiqui et al. 2016).

Procedure management

The patient, under general anaesthesia, is placed in dorsal lithotomy (Blazevski, A. et al. 2020). A Foley catheter is inserted to maintain bladder drainage during the procedure. Antibiotics to prevent infection and muscle relaxants are administered. Depending on the size, shape and location of the tumour, 3 to 6 electrodes are inserted transperineally into the prostate using transrectal ultrasound (TRUS) imaging. According to the applicant's experts, patients selected for IRE have highly visible lesions that generally do not require MRI-TRUS fusion imaging.

Electrodes are positioned in a parallel configuration with a minimum spacing of 1 cm around the tumour tissue, carefully avoiding critical structures such as the urethra, neurovascular bundle, urinary sphincter and rectum. A series of short, high-voltage electrical pulses is then delivered (70–100 µs in length, up to 90 pulses per electrode pair, 20–40 A, 1,500–3,000V/cm) (Faiella et al. 2024; Liu et al. 2024). The patient's cardiac activity, the ablation zone and changes in tissue resistance are monitored intraoperatively by the surgeon. Once IRE is complete, the patient is transferred to the postoperative recovery area until ready for discharge.

IRE is performed by urologists or urologic oncologists, with an operating time of 45 to 60 minutes. The procedure is available in both private and public hospital inpatient settings, with patients admitted due to the requirement for general anaesthesia. The applicant stated that IRE can also be performed in day-surgery centres in certain cases. Work or normal daily activities cannot be performed for up to a week

after the procedure. The applicant's experts stated that treatment failure in focal therapy is typically defined after 2 rounds of treatment (Rodríguez-Sánchez et al. 2024). However, in the Prostate Cancer IRE Study (PRIS), treatment failure was defined as the diagnosis of ISUP grade group ≥2 prostate cancer detected in a 12-month biopsy following IRE (Lantz et al. 2023).

IRE technique

In the literature, IRE is still considered an investigational procedure, subject to operator skills and without a standardised treatment protocol (Cornford 2024; Morozov et al. 2020; Rokan & Reddy 2025). This could lead to inconsistent ablation areas and varying degrees of treatment efficacy across different centres and clinicians.

IRE performance depends on electrode configuration (number, placement and spacing), pulse parameters (pulse repetition; length, interval and amplitude of applied voltage) and tissue heterogeneities, but no consensus has been reached on optimal surgical parameters (Campelo et al. 2017; Jourabchi et al. 2014; Liu et al. 2024). Only a few hospitals have experience with IRE in Australia, which limits opportunities for hands-on learning.

According to the applicant's experts, the IRE protocol is well-standardised in Australia and Aotearoa New Zealand and IRE has been used for over a decade in some centres. Training is provided by the applicant (Getz Healthcare Pty Ltd), consisting of an online seminar by an expert clinician, followed by case observation workshops with key opinion leaders. Practical cases, usually 5 in number, are then performed under the supervision of experienced mentors and applicant technology representatives. The experts highlighted that most urologists already have the necessary skillset to perform IRE, as it requires the same skills as those used for transperineal biopsies. The learning stage involves placing the electrodes around the tumour with a margin and ensuring that the settings are safe (e.g. electrode placement, delivery, energy settings) (personal communication, pre-PASC meeting, 18 February 2025). The on-screen display and initial pulses, used to confirm or adjust parameters, ensure that the energy settings are correct.

Post-IRE procedure follow-up

Similarly to postoperative care following RP, the Foley catheter is removed 2 to 5 days after IRE. In addition to a hospital setting, this procedure (i.e. catheter removal) may also be provided by a practice nurse in primary care or within specialist rooms, according to the Department. Patients then undergo a follow-up consultation with their urologist at 6 weeks to assess for any major adverse effects. Unlike RP, where PSA levels typically drop to undetectable levels and routine imaging is unnecessary, IRE preserves a portion of the prostate, necessitating ongoing surveillance (Yaxley et al. 2022). As a result, follow-up care for IRE closely aligns with active surveillance protocols, although there is no universally standardised protocol, as clinical practice varies among urologists (personal communication, pre-PASC meeting, 18 February 2025). The general approach aligns with international urological guidelines, typically involving PSA testing every 3 months during the first year, an MRI at 6 months and a biopsy at 12 months (Cornford 2024) (NICE 2019). If no abnormalities are detected, PSA testing continues every 6 months, with an MRI every 2 years (Cornford 2024) (NICE 2019). PSA level is an indicator that allows imaging examinations to be undertaken earlier than planned, but it does not constitute a therapeutic decision in itself (Lam et al. 2019). A biopsy is only performed in response to a sudden rise in PSA levels or abnormalities on MRI, and after discussion with the patient (Lam et al. 2019).

According to the applicant's experts, while PSA levels generally decrease post-operation they are not considered a reliable marker of residual disease, and MRIs and biopsies remain essential for ongoing monitoring (Morgan 2024; Tracey et al.). Some clinicians incorporate PSMA PET/CT scans as a supplementary tool for detecting residual or recurrent disease (Yaxley et al. 2022), but, as with follow-up MRIs, these scans remain an out-of-pocket cost for patients due to the absence of Medicare reimbursement for monitoring post-treatment.

The applicant's experts pointed out that treatment failure in focal therapy is typically defined after 2 rounds of treatment (personal communication, pre-PASC meeting, 18 February 2025) (Rodríguez-Sánchez et al. 2024). Approximately 10% of patients require a second IRE procedure, with around 60% of these avoiding progression to whole-gland therapy (personal communication, pre-PASC meeting, 18 February 2025). While outcomes for salvage IRE are not as favourable as for primary IRE—likely due to fibrosis affecting tissue conductivity—the procedure remains effective, achieving local oncological control and reducing treatment-related toxicity and morbidity compared to RP (Blazevski et al. 2023; Geboers et al. 2023; Gielchinsky & Lev-Cohain 2023; Scheltema et al. 2017; Yaxley et al. 2022). The applicant stated that IRE provides an additional salvage therapy option comparable to RP and RT, with approximately 30% of patients requiring secondary treatments after 8 years (Scheltema et al. 2023).

Clinical guidelines and consensus

Focal therapy for prostate cancer involves minimally invasive techniques aimed at selectively ablating cancerous tissue while preserving surrounding healthy structures, with modalities including HIFU, cryotherapy, IRE, laser, photodynamic therapy and brachytherapy (Ong, S et al. 2023). Guidance is limited within current treatment guidelines, although consensus statements have been published on its application.

The key points of current guidelines on focal therapies for prostate cancer are summarised as follows (Ong, S et al. 2023):

- EAU guidelines acknowledge focal therapy as an emerging treatment option for localised prostate cancer but do not currently recommend its use outside of clinical trials.
- NCCN guidelines do not endorse focal therapy as a standard treatment, emphasising the need for more robust data on long-term outcomes.
- The American Urological Association (AUA) guidelines consider focal therapy as investigational, advising that patients should be informed about the limited evidence regarding its efficacy and safety.
- The German S3 guidelines for focal therapy in localised prostate cancer recommend that the available data are insufficient to assess the oncological effectiveness and safety of focal IRE, in particular concerning long-term outcomes (Evidence-based recommendation – agreement 97%).

The multidisciplinary European and NCCN guidelines both acknowledge HIFU and cryotherapy as local therapy options for recurrent prostate cancer after RT (Ong, S et al. 2023). The European guidelines emphasise that these treatments should be reserved for highly selected patients with biopsy-confirmed local recurrence, preferably within a clinical trial or well-designed prospective cohort study at experienced centres (strong recommendation). They highlight that the data on focal therapy were very limited, as focal therapy was involved in less than 15% of the cases reviewed in systematic reviews, with the majority of

cases focusing on whole-gland ablation. In contrast, the NCCN guidelines recommended only cryosurgery and HIFU in the absence of metastatic disease.

The FocAL therapy CONsensus (FALCON) for localised prostate cancer provides guidelines for patient selection and therapeutic approaches, without elaborating on specific techniques (Rodriguez-Sanchez et al. 2025; Rodríguez-Sánchez et al. 2024). Life expectancy, PSA levels, histopathology and lesion accessibility are crucial factors in determining eligibility for focal therapy. Examples of the main statements that reached consensus are as follows:

- Focal therapy should not be offered to ISUP 1 or ISUP >3 patients who prefer active surveillance, but can be considered for those with ISUP 2 and 3, particularly if cribriform patterns are present.
- Prostate volume is irrelevant if the lesion can be reached safely.
- Local clinical stage should be based on MRI; PSMA PET-CT is not recommended for patient selection.
- Focal therapy should not be offered to patients with negative MRI and positive biopsies, or to those for whom MRI is unavailable or is of low quality.
- Follow-up includes functional and oncological outcomes assessed via PSA tests, MRI and biopsies for up to 10 years.
- Patients may be offered more than one salvage focal therapy if the initial one fails.

As FALCON includes all focal therapy techniques, some statements within its guidelines are irrelevant to this application.

The National Institute for Health and Care Excellence (NICE) recommends that IRE 'should only be used with special arrangements for clinical governance, consent and audit or research.' Based on limited evidence, including 1 systematic review, 1 non-RCT and 5 case series, IRE was considered to be effective and safe in the short and medium term, with potential complications and long-term results uncertain (NICE 2023). No population restriction has been defined.

Potential AEs that could arise after IRE include but are not limited to erectile dysfunction, decreased ejaculatory function, urinary retention, urinary incontinence, urinary tract infection, haematuria and rectourethral fistula (NICE 2023).

PASC noted that existing guidelines currently consider IRE an investigational or emerging treatment.

PASC noted that the post-procedural follow-up for IRE differs from that for RP, as IRE preserves the prostate, necessitating ongoing surveillance (PSA; imaging), which closely aligns with active surveillance protocols.

PASC noted the applicant's expert opinion that cognitive fusion can perform as well as software-assisted fusion in the hands of experienced urologists. PASC also noted the importance of visibility on MRI imaging; some patients may have visible lesions on MRI but not on ultrasound, but with cognitive or TRUS fusion, lesions can be identified based on MRI.

Comparator(s)

PICO Set 1 population – ISUP grade 2/3

For patients with localised unifocal intermediate-risk prostate cancer (ISUP grade 2/3) and life expectancy >10 years, RP and RT are the gold standard approaches for treating organ-confined prostate cancer, with RT, particularly brachytherapy, being more suitable for patients with good urinary function (Cornford 2024).

PICO Set 1 population – ISUP grade 1

According to the EAU guidelines, treatment options for standard low-risk prostate cancer (ISUP grade 1, Gleason score 6) are determined by life expectancy, aiming to delay curative treatment without affecting overall survival. Active surveillance is SoC for patients with life expectancy >10 years. However, it is not applicable for the high-risk features population, which is the population described in this PICO (personal communication, pre-PASC meeting, 18 February 2025) (Sanda et al. 2017).

Other individual clinical factors, such as family history and comorbidity, may be able to aid in prostate cancer risk assessment and personalised management (Cornford 2024). During the pre-PASC meeting on 18 February 2025, local experts suggested that some patients with low-risk prostate cancer and life expectancy >10 years may have high-risk features, such as strong family history of aggressive prostate cancer and/or MRI-visible lesions or PET-positive findings. These patients are generally excluded from active surveillance protocols and may require RP and single modality RT (personal communication, pre-PASC meeting, 18 February 2025) (Sanda et al. 2017).

PICO Set 2 population

For patients with localised unifocal recurrence prostate cancer after RT (PICO Set 2), the applicant proposed that the appropriate comparator is SoC, including RP and RT (MSAC application 1794, PICO Set, p.7). According to EAU guidelines, recommended treatment options for radiotherapy failure include RP, brachytherapy and SBRT (Cornford 2024). Conversely, HIFU and cryotherapy are not recommended or funded in Australia for prostate cancer and thus are not considered appropriate comparators, although both are recommended by NCCN guidelines (Ong, S et al. 2023).

Overview

Active surveillance is not included as a comparator in this PICO because it is not considered SoC for the target populations. The target populations, with a relatively high risk of progression and a life expectancy >10 years, are typically unsuited for conservative management (e.g. active surveillance). As such, the SoC is active treatment (i.e. RP or RT).

For all eligible patients with a documented diagnosis and risk stratification of prostate cancer based on prostate biopsy and/or MRI/PET, a multidisciplinary team consensus should be established before proceeding with either the IRE procedure or comparators to ensure a well-coordinated treatment plan (personal communication, pre-PASC meeting, 18 February 2025). Across all subpopulations in this PICO, IRE is positioned as a replacement for the established SoC, either RP or RT. All comparators are currently included on the MBS for use in prostate cancer (as below).

In current practice, the choice between RP and RT is influenced by multiple factors, including patient age, tumour size, potential side effects, patient preference and psychological state (Aizer, Paly & Efstathiou 2013; Nazim et al. 2018; Sanda et al. 2017). It is generally agreed across guidelines that brachytherapy is suitable for patients with good urinary function (Cornford 2024; Sanda et al. 2017). According to AUA

guidelines, RP may be preferred for younger patients with localised prostate cancer over older patients (Sanda et al. 2017). Overall, there are no definitive criteria guiding the selection of comparators; multidisciplinary team consensus is required (Nazim et al. 2018).

According to the applicant's experts, other focal or whole-gland therapies, including HIFU, cryotherapy and laser ablation, are not appropriate comparators. The clinicians stated that these treatments are not publicly funded SoC treatments for prostate cancer; they have limited evidence for efficacy or are rarely used in Australia (personal communication, pre-PASC meeting, 18 February 2025). Additionally, the NICE guidelines recommend against offering HIFU or cryotherapy to patients with localised prostate cancer, due to a lack of evidence on quality of life and long-term survival outcomes (NICE 2019).

Radical prostatectomy

Overview

As a whole-gland radical surgery, RP aims for the complete removal of the entire prostate gland. During the procedure, the prostate gland, along with adjacent tissue including seminal vesicles and vas deferens, is removed. The urethra is severed just above and below the prostate, and the bladder is reconnected to the urethra to restore urinary continuity. For the population included in this application, who have localised cancer, nearby lymph node removal (i.e. pelvic lymph node dissection) is not required, because the cancer has not spread beyond the prostate.

Operative procedure

RP can be performed with open RP, or laparoscopic RP (LRP) or robotically assisted laparoscopic prostatectomy (RALP) approaches:

Open RP: Open surgery can be performed using 2 approaches, retropubic (or suprapubic) prostatectomy and perineal prostatectomy.

- In **retropubic (or suprapubic) prostatectomy**, the surgeon makes an incision in the lower abdominal wall to remove the prostate. This incision is typically approximately 8 cm in length and may extend from below the umbilicus to the top of the pubic hairline or run horizontally across the top of the pubic hairline (Prostate Cancer Foundation of Australia 2023).
- In **perineal prostatectomy**, the prostate is removed via an incision in the perineum (i.e. between the scrotum and anus). This involves a smaller incision and a shorter operation time, so it typically leads to less pain and faster recovery (American Cancer Society 2023); however, it is used less frequently than the retropubic approach because it makes nerve preservation more challenging and may cause erection problems (American Cancer Society 2023).

LRP: Laparoscopic surgery is a minimally invasive alternative to open surgery, performed with or without robotic assistance (NICE 2019). The approach can be either transperitoneal or extraperitoneal (National Institute for Health and Care Excellence 2006). The technique involves keyhole surgery, where several small incisions are made in the lower abdomen. In manual surgery, a laparoscope with other surgery instruments is inserted, providing a clear view for the surgeon to accurately remove the prostate (Prostate Cancer Foundation of Australia 2023). RALP is also performed using the Da Vinci robot system, with the surgeon operating and controlling the robotic arms that hold the tools from a console within the operating theatre (Prostate Cancer Foundation of Australia 2023).

General anaesthesia is usually required for these RP surgery approaches, including open RP, LRP, and RALP. Operation duration is usually 2 to 4 hours, depending on the procedure used (Prostate Cancer Foundation

of Australia 2023). After removal of the prostate, a urinary catheter is inserted into the bladder to assist with bladder drainage. The catheter typically remains in place for 1 to 2 weeks during the healing process until normal urination can resume (American Cancer Society 2023). Postoperative hospitalisation usually lasts 1–5 days, with activity restrictions for several weeks (2–6 weeks), possibly longer for patients with open surgery (Prostate Cancer Foundation of Australia 2023). Pain relief medications may be needed for several weeks after surgery to manage the pain (Brisbane Urology Clinic 2021).

Follow-up

After RP, an undetectable PSA level of <0.2 is typically expected, as all PSA-producing tissue is removed. Follow-up begins on the date of RP and includes PSA test, MRI and biopsy. Local experts recommend PSA testing every 3 months during the first year, an MRI at 6 months and a biopsy at 12 months. If all results are negative, PSA testing will move to 6-monthly, with an MRI every 2 years. The currently recommended frequency of PSA tests after RP, as advised by the applicant's experts, aligns with the NICE guidelines and a peer-reviewed PSA kinetics-based algorithm (Wilkinson, Brundage & Siemens 2008). If any results are positive, active surveillance or further treatment will be considered as needed.

Safety

After RP, common AEs include urinary incontinence, erectile dysfunction and postoperative swelling of the penis and scrotum (National Institute for Health and Care Excellence 2006). The surgery results in infertility. Occasionally, patients may experience permanent urinary incontinence, infection, bowel blockage and death (Brisbane Urology Clinic 2021; Prostate Cancer Foundation of Australia 2023).

Compared with open surgery, LRP and RALP may result in less pain, reduced intraoperative blood loss, shorter length of hospital stay and shorter time of urinary catheter use (American Cancer Society 2023). Studies over decades support these findings (Anastasiadis et al. 2003; Ilic, D et al. 2017; Rassweiler et al. 2003). A prospective study comparing functional outcomes after retropubic RP (n = 70) and LRP (n = 230) performed by different surgeons found that catheterisation duration was significantly shorter for the LRP group (5.8 days vs 7.8 days, p = 0.0006) (Anastasiadis et al. 2003). A Cochrane analysis reported that LRP and RALP are associated with reduced postoperative pain, shorter length of hospital stay and lower transfusion rates compared with open RP (Ilic, D et al. 2017). A retrospective study eliminating surgeon-related factors by analysing 100 RALP and 100 RRP procedures performed by a single surgeon found similar results (Simsir et al. 2021). The RALP group had significantly less blood loss (150 ml vs 328 ml, p<0.001), a lower blood transfusion rate (2% vs 12%, p = 0.021) and a reduced reoperation rate (0% vs 6%, p = 0.001) (Simsir et al. 2021).

A 2023 meta-analysis of RCTs (n = 4) and non-randomised studies (n = 42) suggested that RALP offers potential advantages over LRP in perioperative outcomes, while significantly improving functional recovery, particularly in continence and erectile function (Ma et al. 2023). Meta-analysis of the RCTs found no significant differences between RALP and LRP in terms of blood loss, catheter indwelling time and complication rate (Ma et al. 2023). However, findings from a synthesis of non-randomised studies showed that RALP is associated with reduced blood loss, shorter catheter indwelling time, shorter length of hospital stay, and lower transfusion and complication rates compared with LRP (Ma et al. 2023).

Efficacy

Regarding treatment efficacy, guidelines and evidence including a Cochrane systematic review (Ilic, DE, S. M.; Allan, C. A.; Jung, J. H.; Murphy, D.; Frydenberg, M. 2018) found comparative effectiveness of LRP or RALP compared with open RP for oncological outcomes including recurrence and mortality (American Cancer Society 2023; Prostate Cancer Foundation of Australia 2023). A prospective non-randomised study

(LAPPRO) conducted in 2020, found the cancer recurrence rate between RALP (14%) and open RP (16%) 6 years after surgery was also not significantly different (Nyberg et al. 2020). When comparing RALP and LRP, evidence tends to favour RALP. For example, a systematic review and meta-analysis found a lower biochemical recurrence rate following RALP (RR, 0.59; 95% CI, 0.48–0.73; I^2 = 21%; p<0.00001) (Lee et al. 2017). A meta-analysis of non-randomised studies (n = 78) supported this, showing that biochemical recurrence-free survival was better with RALP compared to RRP (OR:1.33, p = 0.04) (Tang et al. 2017).

MBS items

RP without pelvic lymphadenectomy is covered under MBS item 37210 (Table 5). This aligns with the item included in the application. The schedule fee is $1,815.35 (updated 1 July 2024). MBS item 37213 covers salvage RP without lymphadenectomy after previous RT or ablative focal therapy. The higher schedule fee is $2,722.75 (updated 1 July 2024), which recognises the increased difficulty and risks associated with the procedure and postoperative care compared to standard RP. Both MBS items 37210 and 37213 are approach-agnostic, meaning they can apply to any RP technique, including open RP, LRP and RALP.

MBS item 37211, included in the application, is not considered an appropriate MBS item because it focuses on regional (or locally advanced) disease with pelvic lymphadenectomy. MBS item 37200 is irrelevant, as it refers to a simple or standard prostatectomy (partial or complete removal of the prostate), most commonly used for benign prostatic hypertrophy.

Table 5 Relevant MBS items for radical prostatectomy

Category 3 – THERAPEUTIC PROCEDURES
MBS item 37210 Prostatectomy, radical, involving total excision of the prostate, sparing of nerves around the prostate (where clinically indicated) with or without bladder neck reconstruction, other than a service associated with a service to which item 30390, 30627, 35551, 36502 or 37375 applies Multiple Operation Rule (Anaes.) (Assist.) **Fee**: $1,815.35 Benefit: 75% = $1,361.55
MBS item 37213 Prostatectomy, radical, involving total excision of the prostate, sparing of nerves around the prostate (where clinically indicated): (a) complicated by: (i) previous radiation therapy (including brachytherapy) on the prostate; or (ii) previous ablative procedures on the prostate; and (b) with bladder neck reconstruction; other than a service associated with a service to which item 30390, 30627, 35551, 36502 or 37375 applies Multiple Operation Rule (Anaes.) (Assist.) **Fee**: $2,722.75 Benefit: 75% = $2,042.10

Source: www9.health.gov.au/mbs/, revised based on (MSAC application 1794, PICO Set, p.6)

Radiation therapy

Overview

RT—an alternative radical local therapy for the target population with prostate cancer—is another comparator. RT destroys prostate cancer cells by the application of radiation locally to induce cellular toxicity (Zeman, Schreiber & Tepper 2020). It can be delivered externally via EBRT or internally via brachytherapy (low- or high-dose rate), depending on clinical needs and assessment. EBRT is a non-invasive option compared with surgery (i.e. RP) or brachytherapy.

EBRT is recommended in both EAU and NCCN guidelines for low- to intermediate-risk patients (Cornford 2024; Schaeffer et al. 2024). In Australia, intensity modulated radiation therapy (IMRT) and SBRT are 2 types of commonly used EBRT (Cancer Australia 2025). According to the applicant's clinical experts, proton therapy is not used in Australia (personal communication, pre-PASC meeting, 18 February 2025). It was further confirmed by the Department that there is currently no proton therapy centre in Australia (the Australian Bragg Centre for Proton Therapy and Research is currently under development). As a result, patients would need to travel overseas to access proton therapy. Even if it becomes available domestically, it would not be publicly funded under the MBS or included in the list of eligible cancers for public funding, as outlined in a previous MSAC application (1638).

Primary RT options for low- to intermediate-risk prostate cancer include IMRT, IMRT plus brachytherapy (low- or high-dose rate) and low-dose rate (LDR) brachytherapy, according to current guidelines (Cornford 2024; Sanda et al. 2017). Androgen deprivation therapy (ADT) combined with RT is recommended for select patients, typically those with life expectancy of 5–10 years (Cornford 2024). Therefore, this combination treatment has been excluded for the target population of this PICO, which has life expectancy >10 years, also as per local experts. However, neoadjuvant short-term (4–6 months) ADT is often required to down-regulate hormones before RT (MSAC application 1794, PICO Set, p.12 and 14) (Cornford 2024).

If cancer recurs after RT, salvage RT includes SBRT, LDR brachytherapy and high-dose rate (HDR) brachytherapy (personal communication, pre-PASC meeting, 18 February 2025) (Cornford 2024; Valle et al. 2021).

The guidelines and PICO align well. While the applicant broadly mentioned EBRT and brachytherapy, the PICO provides a more detailed classification based on guidelines and expert input.

Operative procedure

1. **EBRT**

- **IMRT**

  In Australia, IMRT in combination with image-guided RT (IGRT) remains the SoC for treatment of prostate cancer, consistent with the current standard treatment approach for EBRT as suggested by EAU guidelines (Cornford 2024). Multileaf collimators are used to adjust radiation distributions to maximise the radiation dose to target the tumour and spare organs at risk, such as the bladder and rectum (Gorayski, Pinkham & Lehman 2015). IMRT requires at least 20 fractions delivered over 4 to 10 weeks (Schaeffer et al. 2024).

  IMRT is used for conventional fraction and hypofractionation radiation schedules, with hypofractionated radiotherapy recommended as the preferred option, due to comparable effectiveness and improved quality of life (QoL) compared to conventional radiotherapy (NICE 2019). Conventional fraction radiation schedule consists of 1.8–2 Gy per fraction every day; moderate hypofractionation is RT with 2.5–3.4 Gy per fraction; ultra-hypofractionation is defined as RT with >3.4 Gy per fraction (Cornford 2024).

- **SBRT**

  SBRT is a photon-based therapy that precisely targets the tumour using multiple radiation beams. It delivers a high dose of radiation in 1 to 5 treatment fractions over 2 weeks, with higher accuracy compared to IMRT (Schaeffer et al. 2024). A treatment fraction typically takes about 30 minutes, including patient set-up and radiation delivery (Tsang 2016).

2. **Brachytherapy**
   Brachytherapy is the implantation of sealed radioactive seeds inside or close to the tumour in the prostate gland to cause toxicity to the tumour cell. Brachytherapy can be used in patients with good urinary function as a curative therapy for unifocal prostate cancer by itself or it can be combined with EBRT as a boost in unfavourable intermediate- or high-risk cases (Cornford 2024; Schaeffer et al. 2024). Use of brachytherapy is less common than EBRT for the PICO population (South Australian Prostate Cancer Clinical Outcomes Collaborative 2023) and it is not available in all hospitals (Kalli Spencer 2021). Low- or high-dose rate brachytherapy methods are currently used in Australia.

- **LDR brachytherapy**
  The LDR method permanently implants 80 to 120 low-dose radioactive seeds (commonly iodine-125) into the prostate gland, delivering radiation over weeks or months (Cornford 2024). The insertion procedure, guided by rectal ultrasound, is performed under general anaesthesia and typically takes up to 2 hours to complete (Cancer Institute NSW 2015). An overnight stay is required. Before the surgery, an initial day procedure is needed for treatment planning, which also involves general anaesthesia and rectal ultrasound (MSAC application 1794, PICO Set, p.13).

- **HDR brachytherapy**
  The HDR method uses temporary catheters or needles to place high-activity radiation seeds (iridium-192) into the prostate for a few minutes at a time, with multiple sessions (usually 1–4) for repeat doses (Cornford 2024). The procedure is performed under general anaesthesia. The needles and seeds remain in place until treatment is complete. It requires an overnight hospital stay, during which patients must remain in bed (Radiation Oncology Targeting Cancer 2024). Before and during treatment, imaging scans such as ultrasound, CT and MRI are conducted (Mayo Foundation for Medical Education and Research 2023; Mendez & Morton 2018).

Follow-up

After completion of RT, it is recommended by the applicant's experts that patients are evaluated every 6 to 12 months with PSA testing and MRI (personal communication, pre-PASC meeting, 18 February 2025). The application suggested that this follow-up must be individualised and should be adjusted in the event of symptoms or severe side effects (MSAC application 1794, PICO Set, p.14). Urinary incontinence and other genitourinary issues may require regular monitoring, medications, additional medical procedures or the use of pads or diapers. According to the applicant's experts, a rising PSA level or an abnormal MRI after RT may indicate cancer recurrence, warranting a biopsy for further assessment (personal communication, pre-PASC meeting, 18 February 2025).

Side effects

Compared with RP, RT is associated with a higher risk of proctitis, urinary irritation (more common with brachytherapy than EBRT) and gastrointestinal side effects, but a lower incidence of early erectile dysfunction (Sanda et al. 2017). EBRT has side effects such as gastrointestinal and genitourinary toxicity, including dysuria, urinary frequency, urinary retention, haematuria, diarrhoea, rectal bleeding and proctitis, although the severity was reduced by high-quality RT with newer techniques such as IMRT and SBRT (Cornford 2024; Schaeffer et al. 2024). NCCN guidelines recommend hypofractionated IMRT over conventional fractionated IMRT to reduce patient visits without increasing side effects (Schaeffer et al. 2024). General side effects, such as fatigue, are common with EBRT (Cornford 2024). Acute side effects of

EBRT mostly resolve over time (Cornford 2024). Brachytherapy has lower rates of gastrointestinal and genitourinary toxicity compared to EBRT, but a higher incidence of urine retention was noted for HDR brachytherapy (Cornford 2024).

MBS items

Different MBS items reflect the different RT techniques, with each having specific billing and schedule fee structures based on the complexity and approach of the treatment (Table 6 and Table 7). All relevant MBS fees were updated on 1 July 2024. For EBRT, standard intensity IMRT+IGRT is covered by MBS items 15910 (schedule fee $4,142.70) and 15938 (schedule fee $278.40); complex intensity IMRT+IGRT is covered by MBS items 15914 (schedule fee $5,953.95) and 15940 (schedule fee $306.25). SBRT is covered by MBS items 15920 (schedule fee $6,676.00) plus 15944 (additional IGRT, schedule fee $789.35). Simulation and dosimetry for treatment planning, as well as treatment and image verification are included for each technique.

The main procedure of HDR brachytherapy is covered by MBS item 37227. For specific patient populations with PSA ≤10 ng/mL, LDR brachytherapy is covered by MBS item 37220. Patients with PSA levels 10–20 ng/mL are not covered for LDR brachytherapy, based on the item descriptor. The schedule fee is $644.60 for HDR and $1,189.60 for LDR. Relevant MBS item 15966 for the insertion and removal of implants, applicators, catheters or needles, is billed with the main procedures for both HDR and LDR. LDR brachytherapy is also associated with MBS items 55603, 60506 and 60509 for imaging services.

The application included MBS items 37227, 15944 and 15940, without mentioning any other items. The remaining items, as listed above, await expert feedback and require verification.

Table 6 Relevant MBS items for EBRT

Category 3 – THERAPEUTIC PROCEDURES
MBS item 15910 Megavoltage planning—level 3.1 Standard intensity modulated radiation therapy (IMRT) simulation and dosimetry for treatment planning, if: (a) all of the following apply in relation to the simulation: (i) treatment set-up and technique specifications are in preparation for single-dose level IMRT planning without motion management; (ii) patient set-up and immobilisation techniques are suitable for image volume data acquisition and reproducible IMRT treatment; (iii) a high-quality three-dimensional image volume dataset is acquired in treatment position for the relevant region of interest to be planned and treated with image verification; and (b) all of the following apply in relation to the dosimetry: (i) the IMRT planning process is required to calculate dose to a single-dose level volume structure and requires a dose-volume histogram to complete the planning process; (ii) based on review and assessment by a radiation oncologist, the IMRT planning process optimises the differential between target dose, organs at risk and normal tissue dose; (iii) all relevant gross tumour volumes, clinical target volumes, planning target volumes and organs at risk are rendered as volumes and nominated with planning dose objectives; (iv) organs at risk are nominated as planning dose constraints; (v) dose calculations and dose-volume histograms are generated in an inverse planned process using a specialised algorithm, with prescription and plan details approved and recorded with the plan; (vi) a three-dimensional image volume dataset is used for the relevant region to be planned and treated with image verification Applicable once per course of treatment **Fee**: $4,142.70 Benefit: 75% = $3,107.05 85% = $4,040.30

MBS item 15938

Megavoltage treatment—level 3.1

Standard single-dose level intensity modulated radiation therapy (IMRT) treatment and image verification, without motion management, if:

(a) the treatment is delivered using a device that is included in the Australian Register of Therapeutic Goods; and

(b) image-guided radiation therapy (IGRT) imaging is used to implement a standard IMRT plan at a level that is equivalent to or higher than that described in item 15910

Fee: $278.40 Benefit: 75% = $208.80 85% = $236.65

MBS item 15914

Megavoltage planning—level 3.2

Complex intensity modulated radiation therapy (IMRT) simulation and dosimetry for treatment planning, if

(a) all of the following apply in relation to the simulation:

(i) treatment set-up and technique specifications are in preparation for multiple-dose level IMRT planning or single-dose level IMRT planning requiring motion management;

(ii) patient set-up and immobilisation techniques are suitable for image volume data acquisition and reproducible IMRT treatment;

(iii) a high-quality three-dimensional or four-dimensional volume dataset is acquired in treatment position for the relevant region of interest to be planned and treated with image verification; and

(b) all of the following apply in relation to the dosimetry:

(i) the IMRT planning process is required to calculate dose to multiple-dose level volume structures or single-dose level volume structures (including structures moving with physiologic processes or requiring precise positioning with respect to beam edges) and requires a dose-volume histogram to complete the planning process;

(ii) based on review and assessment by a radiation oncologist, the IMRT planning process optimises the differential between target dose, organs at risk and normal tissue dose;

(iii) all relevant gross tumour targets, clinical target volumes, planning target volumes, internal target volumes and organs at risk are rendered and nominated with planning dose objectives;

(iv) organs at risk are nominated as planning dose constraints;

(v) dose calculations and dose-volume histograms are generated in an inverse planned process using a specialised algorithm, with prescription and plan details approved and recorded with the plan;

(vi) a three-dimensional or four-dimensional image volume dataset is used for the relevant region to be planned and treated, with image verification for a multiple-dose level IMRT planning or single-dose level IMRT planning requiring motion management

Applicable once per course of treatment

Fee: $5,953.95 Benefit: 75% = $4,465.50 85% = $5,851.55

MBS item 15940

Megavoltage treatment—level 3.2

Complex multiple-dose level intensity modulated radiation therapy (IMRT) treatment, or single-dose level IMRT treatment requiring motion management, and image verification, if:

(a) the treatment is delivered using a device that is included in the Australian Register of Therapeutic Goods; and

(b) image-guided radiation therapy (IGRT) imaging is used (with motion management functionality if required) to implement a complex IMRT plan at a level that is equivalent to or higher than that described in item 15914; and

(c) radiation field positioning requires accurate dose delivery to the target; and

(d) image decisions and actions are documented in the patient's record

Fee: $306.25 Benefit: 75% = $229.70 85% = $260.35

MBS item 15920

Megavoltage planning—level 4

Stereotactic body radiation therapy (SBRT) simulation and dosimetry for treatment planning, if:

(a) all of the following apply in relation to the simulation:

(i) treatment set-up and technique specifications are in preparation for inverse planning with multiple non-coplanar, rotational or fixed beam stereotactic delivery or intensity modulated radiation therapy (IMRT) stereotactic delivery;

(ii) personalised patient set-up and immobilisation techniques are suitable for reliable imaging acquisition and reproducible, including techniques to minimise motion of organs at risk and targets;

(iii) small-field and ablative treatment is used;

(iv) a high-quality three-dimensional or four-dimensional image volume dataset is acquired in treatment position for the relevant region of interest to be planned, treated and verified (through daily planar or volumetric image guidance strategies); and (b) all of the following apply in relation to the dosimetry: (i) the planning process is required to calculate dose to single or multiple target structures and requires a dose-volume histogram to complete the planning process; (ii) based on review and assessment by a radiation oncologist, the planning process maximises the differential between target dose, organs at risk and normal tissue dose; (iii) all relevant gross tumour volumes, clinical target volumes, planning target volumes and organs at risk are rendered and nominated with planning dose objectives; (iv) organs at risk are nominated as planning dose constraints; (v) dose calculations and dose-volume histograms are generated using a validated stereotactic-type algorithm, with prescription and plan details approved and recorded with the plan Applicable once per course of treatment **Fee**: $6,676.00 Benefit: 75% = $5,007.00 85% = $6,573.60
MBS item 15944 Megavoltage treatment—level 4 Stereotactic body radiation therapy (SBRT) treatment and image verification, if: (a) the treatment is delivered using a device that is included in the Australian Register of Therapeutic Goods; and (b) image-guided radiation therapy (IGRT) is used (with motion management functionality if required) to implement a stereotactic body radiation therapy plan at a level that is equivalent to or higher than that described in item 15920; and (c) radiation field positioning requires accurate dose delivery to the target; and (d) image decisions and actions are documented in the patient's record **Fee**: $789.35 Benefit: 75% = $592.05 85% = $686.95

Source: www9.health.gov.au/mbs/, revised based on (MSAC application 1794, PICO Set, p.6)

Table 7 Relevant MBS items for brachytherapy

Category 3 – THERAPEUTIC PROCEDURES
MBS item 37220 Prostate, radioactive seed implantation of, urological component, using transrectal ultrasound guidance: (a) for a patient with: (i) localised prostatic malignancy at clinical stages T1 (clinically inapparent tumour not palpable or visible by imaging) or T2 (tumour confined within prostate); and (ii) a Gleason score of less than or equal to 7 (Grade Group 1 to Grade Group 3); and (iii) a prostate specific antigen (PSA) of not more than 10ng/ml at the time of diagnosis; and (b) performed by a urologist at an approved site in association with a radiation oncologist; and (c) being a service associated with: (i) services to which items 15966 and 55603 apply; and (ii) a service to which item 60506 or 60509 applies (H) Multiple Operation Rule (Anaes.) **Fee**: $1,189.60 Benefit: 75% = $892.20
MBS item 37227 Prostate, transperineal insertion of catheters for high dose rate brachytherapy using ultrasound guidance including any associated cystoscopy, if performed at an approved site, and being a service associated with a service to which item 15966 applies (H) Multiple Operation Rule **Fee**: $644.60 Benefit: 75% = $483.45

MBS item 15966 Complex insertion of any of the following kinds of interstitial brachytherapy implants not requiring surgical exposure, with image guidance, and if a radiation oncologist is in attendance during the service: (a) catheters or needles for temporary implants; (b) radioactive sources for permanent implants; (c) breast applicators, single channel and multi-channel strut devices; including the removal of applicators, catheters or needles (Anaes.) **Fee**: $531.95 Benefit: 75% = $399.00 85% = $452.20
Category 5 - DIAGNOSTIC IMAGING SERVICES
MBS item 55603 Prostate, bladder base and urethra, ultrasound scan of, if performed: (a) personally by a medical practitioner who made the assessment mentioned in paragraph (c) using one or more transducer probes that 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: (i) a specialist in urology, radiation oncology or medical oncology; or (ii) a consultant physician in medical oncology; who has: (iii) examined the patient in the 60 days before the scan; and (iv) recommended the scan for the management of the patient's current prostatic disease (R) Bulk bill incentive **Fee**: $122.40 Benefit: 75% = $91.80 85% = $104.05
MBS item 60506 Fluoroscopy using a mobile image intensifier, in conjunction with a surgical procedure lasting less than 1 hour, not being a service associated with a service to which another item in this Group applies (R) (H) Bulk bill incentive **Fee**: $71.50 Benefit: 75% = $53.65
MBS item 60509 Fluoroscopy using a mobile image intensifier, in conjunction with a surgical procedure lasting 1 hour or more, not being a service associated with a service to which another item in this Group applies (R) (H) Bulk bill incentive **Fee**: $110.90 Benefit: 75% = $83.20

Source: www9.health.gov.au/mbs/, revised based on (MSAC application 1794, PICO Set, p.6)

PASC noted RP and RT are the current gold standard approaches for treating organ-confined prostate cancer.

PASC confirmed active surveillance should be included as a comparator for patients with low-grade prostate cancer with high-risk features, as per current guidelines, if this subgroup is included in the target population.

PASC noted other focal therapies may be considered potential near-market comparators rather than true comparators.

Outcomes

The application seeks funding for IRE, based on the premise that the procedure would benefit eligible patients by targeting only the diseased portion of the prostate through focal therapy. This approach aims to reduce the risk of erectile dysfunction and urinary incontinence associated with whole-gland treatment, while maintaining comparable oncological outcomes.

The application provided a list of relevant outcomes for assessing the clinical safety and effectiveness of IRE. This list was reviewed and updated according to the standard set of multidimensional patient-centred health outcomes for localised prostate cancers, developed by the International Consortium for Health Outcomes Measurement (ICHOM) (Martin et al. 2015), and outcomes cited in the following registered clinical trials: NCT06772116 (Maiolino 2025), ACTRN12612000523808 (Earl 2014) and NCT06223295 (te Molder 2024).

The outcomes specified below are consistent across both populations, except for the outcome 'cost of cancer relapse', added for patients with recurrence after RT.

Non-health outcomes were also reviewed to assess the impact of IRE on patients' lives. IRE is available in a limited number of medical centres in Australia, which raises the question of accessibility and equity of treatment for patients in rural and regional areas.

Due to its minimally invasive nature, IRE may lead to reduced recovery time and reduced AEs, enabling patients to remain active within their family, community and workplace with minimal disruption. It may also relieve families of the burden of caring for dependent relatives and assist their mental and emotional wellbeing.

<u>Safety outcomes</u>

- Erectile function – maintenance of potency
- Genitourinary AEs (e.g. urinary incontinence, urinary retention, bowel dysfunction, fistula)
- Treatment-related AEs, measured using either:
    - Clavien-Dindo classification for surgically treated patients (grade ≥3)
    - CTCAE classification for non-surgically treated patients (grade ≥3)

<u>Clinical effectiveness outcomes</u>

- Overall survival
- Cancer-specific survival
- Metastasis-free survival
- Treatment failure (histopathology assessment, MRI)
- Rate of negative in-field biopsy
- Rates of in-field or out-of-field recurrences
- Recovery time
- Need for secondary (i.e. salvage treatment rate) or adjuvant treatment
- PSA levels

- Patient-reported health status (EPIC, IPSS-QoL, IIEF-15, EQ-5D, SHIM)
- Patient satisfaction

Non-health outcomes

- Societal outcomes: workplace productivity and absenteeism, preservation of patient involvement in family and community life with minimal interference, caregiving load and wellbeing
- Ethical and organisational: accessibility of IRE and equity for regional patients

Healthcare resource-use outcomes

- Operating time
- Length of hospital stay
- Costs associated with the intervention and comparators, including cost of post-cancer lesion assessments (e.g. biopsies, specialist appointments, MRI, PSA testing)
- Cost associated with AEs for the intervention and comparators
- Cost of cancer relapse and secondary treatment (PICO set 2 only)
- Cost effectiveness
- Budget impact

Postoperative AEs should be reported according to the Clavien-Dindo classification. ICHOM considers that only grade ≥3 toxicities should be reported (Martin et al. 2015). Genitourinary AEs can also be measured using specific questionnaires, such as the International Prostate Symptom Score (IPSS), which assesses lower urinary tract symptoms.

According to ICHOM, overall survival, cancer-specific survival and metastasis-free survival are key measures of cancer eradication for the standard set of multidimensional patient-centred health outcomes (Martin et al. 2015). These survival and disease control outcomes have a strong correlation with patient anxiety and the initiation of additional therapy, and they should be collected annually until death.

Treatment failure following focal therapy lacks a standardised definition. According to the applicant's expert, it is defined as the inability to achieve the desired therapeutic outcome despite undergoing 2 rounds of treatment (Rodríguez-Sánchez et al. 2024). In the Prostate Cancer IRE Study (PRIS), treatment failure was defined as the diagnosis of ISUP grade group ≥2 prostate cancer detected in a 12-month biopsy following IRE (Lantz et al. 2023).

A negative in-field biopsy assesses the effectiveness of IRE in tumour ablation (Yaxley et al. 2022). The applicant's expert highlighted that routine biopsies are not generally performed after RT or RP, making direct comparisons between IRE and these treatments challenging for this outcome.

Several tools can be used to assess patient-reported outcome measures (PROMs) in prostate cancer patients. The international index of erectile function (IIEF) is a multidimensional scale that evaluates erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction. The sexual health inventory for men (SHIM) is a validated abbreviated version of IIEF widely used in clinics to evaluate and assess treatment efficacy for erectile dysfunction. The expanded prostate cancer index composite (EPIC) score assesses health-related QoL (HRQoL) across urinary, bowel, sexual and hormonal domains. The IPSS-QoL consists of 7 questions on patient-reported lower urinary tract symptoms. Other tools for assessing overall QoL, such as the EuroQol 5-dimension questionnaire (EQ-5D), could also be

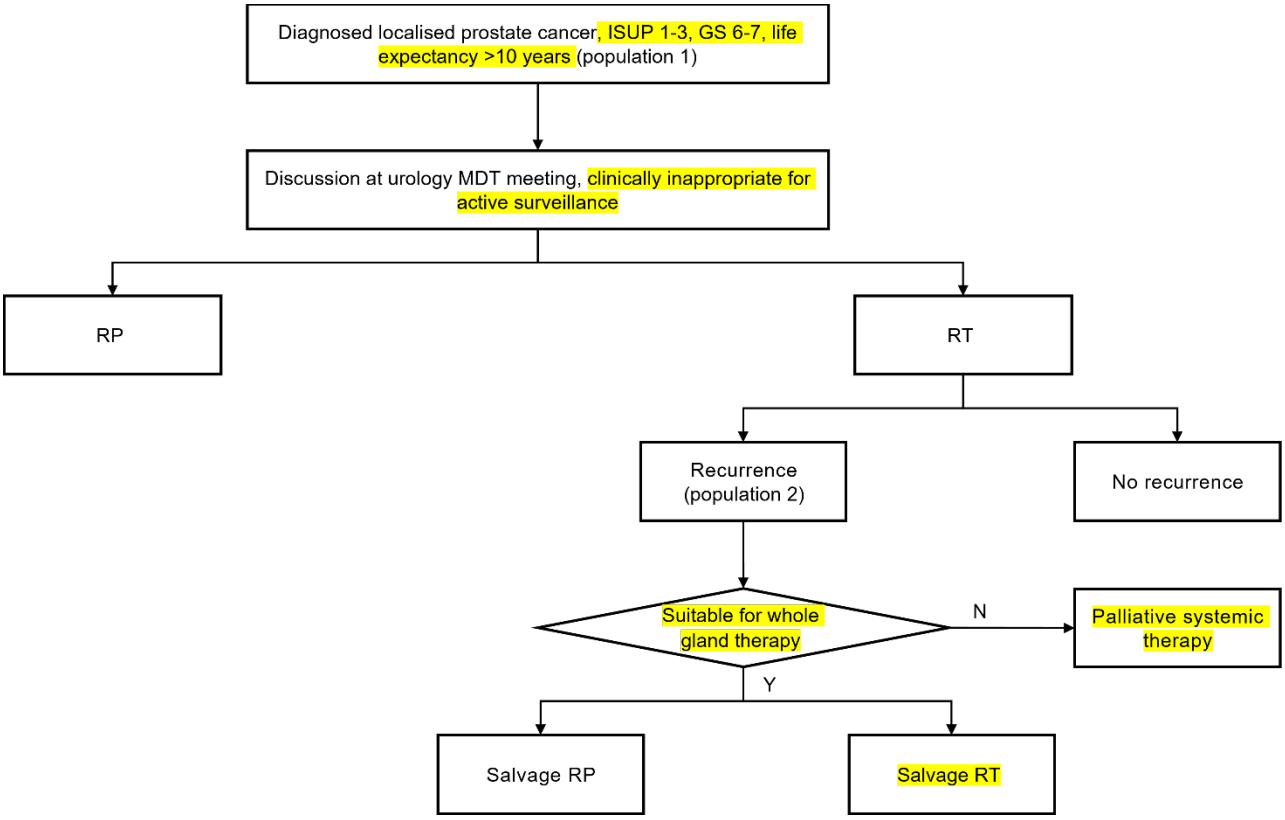
included, as prostate cancer patients often present symptoms beyond the commonly monitored urinary, bowel and sexual domains.

PASC considered that the outcomes would need to be validated through expert input during the assessment.

Clinical management algorithms

The applicant provided the current and proposed clinical management algorithms for the 2 target populations (Figure 1 and Figure 2). These algorithms were reviewed and updated based on feedback from the pre-PASC meeting on 18 February 2025, as well as current guidelines (i.e. NCCN, EAU, NICE). Differences between the algorithms proposed by the applicant and the updated version are highlighted in yellow. The algorithms are presented with the 2 proposed populations in a single figure.

Figure 1 Current clinical management algorithm of initial therapy options for low- and intermediate-risk prostate cancer and salvage treatment options for recurrence after RT



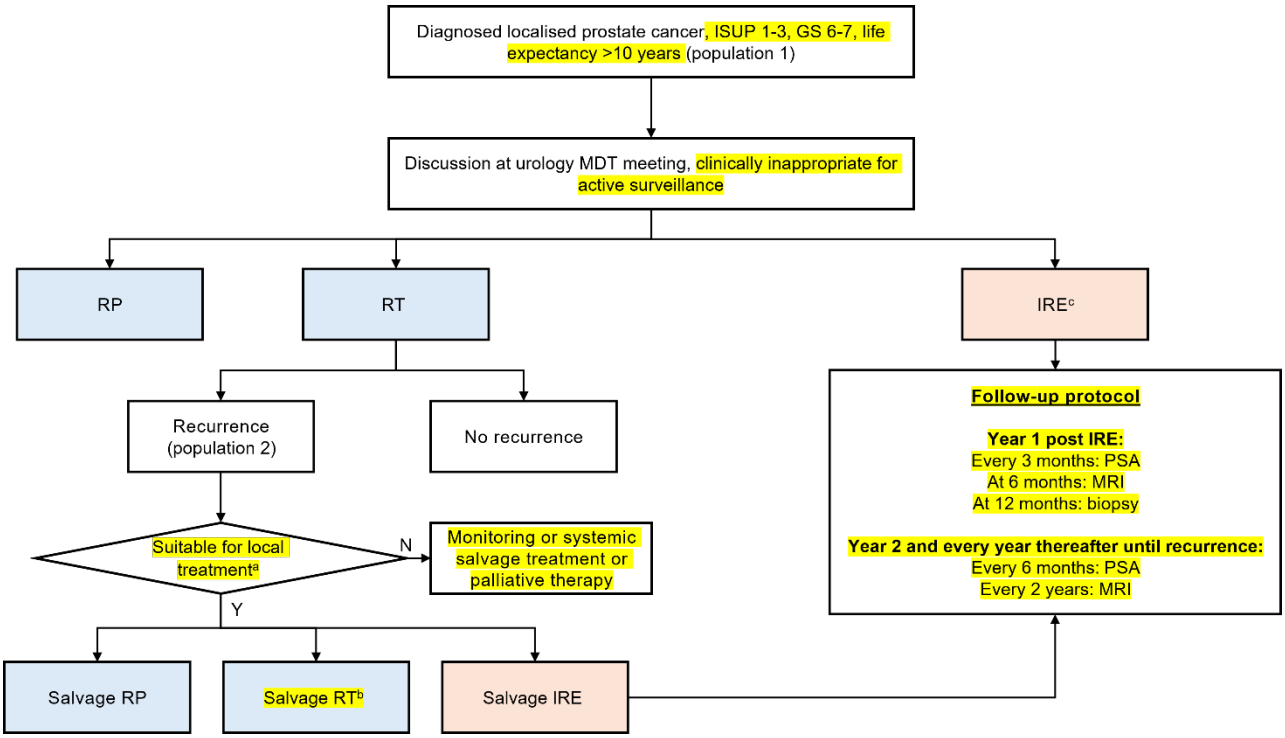
GS = Gleason score; ISUP = International Society of Urological Pathology; MDT = multidisciplinary team; RP = radical prostatectomy; RT = radiation therapy

Yellow = differences between the algorithms proposed by the applicant and the updated version

The current treatment options for populations in PICO Sets 1 and 2 both include RP and RT, considered to be the current SoC. RP can be performed via open RP, LRP and RALP, with RALP being the most commonly used technique in practice (Ong, WL et al. 2024). According to the applicant's experts, primary RT includes IMRT and brachytherapy, whereas SBRT is used exclusively in salvage RT in practice (personal communication, pre-PASC meeting, 18 February 2025). The *Prostate Cancer Across Australia and New*

Zealand Annual Report 2023 provides data on the proportion of initial management in public hospitals (Ong, WL et al. 2024). In 2021, for patients receiving local treatment, 82.4% of those with low-risk prostate cancer underwent RP, while 17.6% had RT. For intermediate-risk prostate cancer, 78.6% received RP and 21.4% received RT (Ong, WL et al. 2024).

Figure 2 Proposed clinical management algorithm of initial therapy options for low- and intermediate-risk prostate cancer and salvage treatment options for recurrence after RT



GS = Gleason score; IRE = irreversible electroporation; ISUP = International Society of Urological Pathology; MDT = multidisciplinary team; RP = radical prostatectomy; RT = radiation therapy
Orange = intervention
Blue = comparator
Yellow = differences between the algorithms proposed by the applicant and the updated version
a Local treatment includes focal therapy or whole gland therapy. Eligibility criteria: local histologically proven recurrence and life expectancy >5 years (Cornford 2024; Schaeffer et al. 2024)
b Salvage radiation therapy includes SBRT and brachytherapy (LDR and HDR) (Cornford 2024; Valle et al. 2021)(personal communication, pre-PASC meeting, 18 February 2025)
c A second IRE procedure may be required in the event of recurrence, provided the same eligibility criteria are met

In the proposed pathway, IRE (intervention) is positioned as an alternative to the established SoC, either for primary or salvage treatment (comparators), including RP and RT. A second IRE treatment, as a form of local secondary therapy, can be used for patients who experience recurrence after primary IRE, provided the same eligibility criteria as for primary IRE are met.

For the recurrence after RT population, EAU guidelines recommend monitoring for patients with low-risk biochemical recurrence; systemic salvage treatment is for those with high-risk, regional or metastatic cancer. According to NCCN guidelines, palliative therapy is recommended for patients with progression and life expectancy <5 years (Schaeffer et al. 2024). Patients with locally confirmed recurrence and life expectancy >5 years are classified as PICO Set 2 and are eligible for local treatments such as salvage RP,

salvage RT and salvage IRE, in accordance with EAU and NCCN guidelines (Cornford 2024; Schaeffer et al. 2024).

PASC noted the algorithms indicate 'clinically inappropriate for active surveillance', making RP or RT SoC.

Proposed economic evaluation

The application claimed that IRE provides superior safety outcomes to RP and RT in the primary treatment of intermediate-grade unifocal localised prostate cancer, as well as in salvage treatment after RT. Several studies showed that patients who underwent IRE had lower rates of incontinence and erectile dysfunction, improved HRQoL and faster recovery times compared to conventional treatments (Blazevski et al. 2023; Blazevski, Alexandar et al. 2020; Flegar et al. 2022; Geboers et al. 2023; Gielchinsky & Lev-Cohain 2023; Scheltema et al. 2018; Scheltema et al. 2023; Scheltema et al. 2017; van den Bos et al. 2018; Yaxley et al. 2022). The application also claimed that IRE for the proposed populations is non-inferior in terms of oncological outcomes, with a similar recurrence rate to conventional treatments (MSAC Application 1794, PICO Set, p.15).

The available evidence consists mainly of retrospective or prospective single-arm studies, with short to medium follow-up periods and small to moderate patient populations. One retrospective study conducted a propensity score-matched analysis comparing cohorts of patients who underwent IRE or robot-assisted RP (Scheltema et al. 2018). A few comparative studies exist, but they either compare focal versus extended IRE ablation or do not report outcomes of interest.

Two ongoing RCTs meeting the defined PICO criteria were identified:

- Partial prostate Ablation versus Radical Treatment (PART) in intermediate risk, unilateral clinically localised prostate cancer (Award ID: 17/150/01) (National Institute for Health and Care Research). This study intended to enrol 800 men and is due to end in October 2026. Depending on how the data are described, the outcome may or may not be usable for this application, given that the intervention consists of either IRE or HIFU. The comparators are RP, radical RT and LDR brachytherapy. The first outcomes should assess primary treatment failure after a median follow-up of ≥3 years after randomisation; and HRQoL as measured by the patient-oriented prostate utility scale (PORPUS-P) at 6 weeks, 3 months, 6 months and 12 months and annually thereafter until the end of the study. Secondary outcomes are HRQoL using standard validated PROMs, healthcare resource utilisation and cost-effectiveness in terms of cost per quality-adjusted life year, serious treatment-related AEs, proportion of patients requiring repeat partial ablation treatment, time to disease progression, and time to disease-specific and overall mortality.
- Prostate Cancer IRE Study (PRIS) (NCT05513443) (Lantz et al. 2023). This trial is scheduled to end in September 2026 with 184 men recruited. It encompasses two parallel RCTs, one comparing IRE with RP and the other comparing IRE with RT. The primary outcomes assess urinary continence and irritative urinary symptoms at 12 months post-operation. The secondary outcomes measure erectile dysfunction, voiding and bowel functions, AEs, QoL (i.e. EQ-5D) and treatment failure.

The clinical claim in the application leads to a cost-effectiveness or cost-utility analysis for the economic evaluation (Table 8).

Table 8 Classification of comparative effectiveness and safety of the proposed intervention, compared with its main comparator, and guide to the suitable type of economic evaluation

Comparative safety-	Comparative effectiveness			
	Inferior	Uncertain[a]	Noninferior[b]	Superior
Inferior	Health forgone: need other supportive factors	Health forgone possible: need other supportive factors	Health forgone: need other supportive factors	? Likely CUA
Uncertain[a]	Health forgone possible: need other supportive factors	?	?	? Likely CEA/CUA
Noninferior[b]	Health forgone: need other supportive factors	?	CMA	CEA/CUA
Superior	? Likely CUA	? Likely CEA/CUA	CEA/CUA	CEA/CUA

CEA = cost-effectiveness analysis; CMA = cost-minimisation analysis; CUA = cost-utility analysis; ? = reflects uncertainties and any identified health trade-offs in the economic evaluation as a minimum in a cost-consequences analysis
Orange colour indicates the selected analysis suitable for the economic evaluation
a 'Uncertainty' covers concepts such as inadequate minimisation of important sources of bias, lack of statistical significance in an underpowered trial, detecting clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or the comparative safety considerations
b An adequate assessment of 'noninferiority' is the preferred basis for demonstrating equivalence

PASC noted the clinical claim for superior safety would lend itself to a cost-effectiveness analysis/cost-utility analysis.

PASC noted the completion dates of the ongoing RCTs. Study completion for the PRIS and PART studies is estimated for September and October 2026, respectively.

Proposal for public funding

The application proposed new MBS items for IRE focal therapy in prostate cancer.

Draft MBS item descriptors proposed in the application for primary and recurrent prostate cancer treatments using IRE are shown in Table 9 and Table 10, respectively. The assessment group suggested amendments (indicated by underlining or strikethrough), following discussion with the applicant and the department (personal communication, pre-PASC meeting, 18 February 2025). The application proposed a fee of $644.60 for each item.

Table 9 Proposed MBS item for primary IRE treatment in patients with localised unifocal intermediate-grade and high-risk features, low-grade prostate cancer (updated to incorporate PASC advice)

Category 3 – THERAPEUTIC PROCEDURES
MBS item AAAA Prostate, irreversible electroporation, using transrectal ultrasound guidance including any associated cystoscopy: a. For a patient with: (i) confirmed histopathological localised prostatic malignancy with a unifocal index tumour visible on imaging (ii) a Gleason score = ~~≤ of less than or equal to~~ 7 ~~(Grade Group 1 to Grade Group 3)~~, ISUP 2 to 3, or (iii) a Gleason score = 6, ISUP 1, clinically inappropriate for active surveillance (iv) a multidisciplinary team has reviewed treatment options for the patient and assessed that focal therapy is suitable (v) a life expectancy >10 years b. Performed by a urologist or a urologic oncologist at an approved site No separate ultrasound or cystoscopy item is payable with this item This MBS item can only be claimed ~~twice~~ once in a patient's lifetime
Fee: ~~$1,815.35~~ $644.60 75% benefit = $483.45

Suggested amendments made by the assessment group are shown in underline or strikethrough. Additionally changes made based on PASC advice are presented in red text.

Source: MSAC 1794 PICO set p.11

Table 10 Proposed MBS item for patients with localised relapsed prostate cancer after radiation therapy (updated to incorporate PASC advice)

Category 3 – THERAPEUTIC PROCEDURES
MBS item BBBB Prostate, irreversible electroporation, using transrectal ultrasound guidance including any associated cystoscopy: a. For a patient with: (i) confirmed imaged and~~/or~~ histopathological ~~recurrent~~ recurrence of localised unifocal prostatic malignancy visible on imaging (ii) Gleason score = 7 ~~(Grade Group 1 to Grade Group 3)~~, or ISUP 2 to 3 (iii) previous radiation therapy (including brachytherapy) on the prostate (iv) a multidisciplinary team has reviewed treatment options for the patient and assessed that salvage irreversible electroporation is suitable (v) a life expectancy >5 years b. Performed by a urologist or a urologic oncologist at an approved site No separate ultrasound or cystoscopy item is payable with this item This MBS item can only be claimed once in a patient's lifetime
Fee: ~~$1,815.35~~ $644.60 75% benefit = $483.45

Suggested amendments made by the assessment group are shown in underline or strikethrough. Additionally changes made based on PASC advice are presented in red text.

Source: MSAC 1794 PICO set p.12

The suggested amendments were proposed by the assessment group to better describe PICO Sets 1 and 2. These include the following:

For proposed MBS item AAAA:

- The term 'unifocal index tumour' was added. This is the terminology employed by the applicant's expert when describing PICO Set 1 (personal communication, pre-PASC meeting, 18 February 2025). This broader term (compared to 'unifocal') allows for greater flexibility in interpretation, rather than being strictly limited to the technical definition. The applicant's expert mentioned 2 examples where IRE could be used:
    - treatment of 2 adjacent foci within the same single ablation field—the expert emphasised that the key consideration is the ability to treat the tumour(s) within a single treatment field;
    - treatment of a localised intermediate-grade prostate cancer even if low-grade tumour tissue is outside the in-field area, allowing for the ablation of the index lesion, which could potentially lead to metastasis.
- Among all patients with low-grade tumour tissue (Gleason score 6, ISUP 1) only those with high-risk features are relevant for this application.

For proposed MBS item BBBB, according to the applicant's experts, only patients with localised unifocal intermediate-grade prostate cancer who have experienced recurrence after radiotherapy would be considered. Low-grade prostate cancer (written as Grade Group 1) has been removed from the proposed MBS item.

The proposed fee was determined in consultation with urologists currently performing the procedure and aligns with the reimbursement amount for one of the comparators, MBS item 37210 (RP) (personal communication, pre-PASC meeting, 18 February 2025). The applicant indicated that the proposed fee includes the cost of live imaging ultrasound guidance (MBS item 55603) and cystoscopy (MBS item 36812) required during the procedure. The proposed wording in the item descriptors has been amended to clarify these inclusions.

The applicant's expert highlighted that patients entirely dependent on a pacemaker are unsuitable for the IRE procedure. A pacemaker or defibrillator with sensing functions can be deactivated during the intervention, resulting in potential issues for the patient.

The application estimated the overall cost per patient at $23,000, including urologist fees, general anaesthesia, hospital costs and follow-up MRI. Hospital admission and stay, consumables, the NanoKnife generator and electrodes (1–6) were incorporated within the hospital costs. According to the application, a standard prostate IRE procedure usually requires 3 to 6 electrodes, transrectal ultrasound guidance for prostate and targeted treatment area visualisation, and a brachytherapy grid to facilitate placement of the electrodes.

The application indicated an estimated out-of-pocket cost of $12,000, reflecting the average cost of electrodes per procedure (MSAC Application, lodgement summary document p.7 and 8). To date, the IRE procedure (and follow-up MRIs) is self-funded by patients.

The application highlighted that an investment cost to purchase ($570,000) or lease the NanoKnife generator system must also be taken into account by the hospital.

The electrodes (ARTG ID 205431) and the electrosurgical system generator (ARTG ID 205432) are not registered on the Prescribed List of Medical Devices and Human Tissue Products. The applicant indicated intent to lodge an application for funding of the electrodes under the Prescribed List.

PASC advised that it should be specified for PICO Set 1 population that disease must be evident on imaging. This is based on advice from the applicant's clinical experts that disease must be visible on MRI (or an MRI surrogate such as PSMA PET).

Regarding the item descriptors, PASC considered the following:

- *tumour visibility on imaging should be included in the item descriptor. PASC considered that type of imaging should be defined in an explanatory note referencing in greater detail the imaging expectations.*
- *the treatment frequency should be limited to once per lifetime, unless supportive evidence is presented. PASC noted the FALCON consensus statement recommends that 'patients may be offered more than one salvage focal therapy if the initial procedure fails.'*

PASC also discussed the fees for:

- *MRI. The applicant's clinical experts indicated that for most patients their pretreatment MRI is either their initial diagnostic work-up MRI (MBS item 63541) or a routine interval scan for active surveillance that demonstrates disease progression (MBS item 63543). The Department advised that not all IRE patients will be eligible for a rebate under MBS items 63541 and 63543, and no MBS item exists for MRI after focal therapy. PASC noted there is no MBS item for a post-treatment monitoring MRI. PASC noted that addressing the existing gaps was not part of the current application.*
- *Surgical assistant. The experts confirmed that support is required—either from an assistant or well-trained nursing staff—to ensure correct electrode connections, settings and measurements. PASC noted assistant costs should be included in the assessment.*
- *Proposed MBS items. PASC considered the IRE procedure is more aligned with HDR brachytherapy than RP, with brachytherapy requiring the insertion of seeds or wires, as well as the use of transrectal ultrasound. The revised proposed fee based on item 37227 would be $644.60 (75% benefit = $483.45).*

PASC advised the applicant to seek advice from the Prescribed List team regarding in-principle eligibility of the electrodes for the Prescribed List.

Summary of public consultation input

PASC noted and welcomed consultation input from 11 organisations and 34 individuals, 28 of whom were consumers and 6 health professionals. The 11 organisations that submitted input were:

- Prostate Cancer Foundation of Australia (PCFA)
- Royal Australian and New Zealand College of Radiologists (RANZCR)
- Urologic Society of Australia and New Zealand (USANZ)
- Noosa Prostate Association
- Eltham Prostate Cancer Information and Support Group
- Port Macquarie Prostate Cancer Support Group
- Victorian Council of Prostate Cancer Support Groups
- Geelong Prostate Support Group
- Maryborough (Qld) Prostate Cancer Support Group

- Moreton Bay Regional Prostate Cancer Support Group
- Shoalhaven Prostate Cancer Support Group

The consultation input received was largely supportive of public funding for IRE for prostate tumour tissue in patients with prostate cancer.

Consumer Input

Most of the consumer input came from individuals who had been treated for prostate cancer, some of whom had been treated with IRE. Some consumers noted that whilst the procedure had not been successful for them, they still considered that it was a valuable option for people with prostate cancer to be able to access. Consumers noted the emotional and social toll that the side effects of incontinence and erectile dysfunction from conventional treatment can have, and the importance of having the option of IRE to potentially avoid these side effects.

Benefits and Disadvantages

The main benefits of public funding received in the consultation input included that IRE is less invasive, associated with rapid recovery and has lower rates of incontinence and erectile dysfunction compared to conventional treatment. PCFA stated that IRE is extremely reliable in destroying tumour tissue and USANZ stated that there is good long-term data supporting the use of focal therapy in carefully selected patients.

The main disadvantage of public funding received in the consultation input was concerns that IRE would be inaccessible due to limited locations providing the service and potential out of pocket costs. RANZCR stated that more robust data, ideally from randomised clinical trials, was required to provide evidence of long-term quality of life and patient outcomes.

Population, Comparator (current management) and Delivery

The consultation input largely agreed with the proposed population. RANZCR noted the proposed population is overly broad. A health professional reflected that whilst prostate cancer is most common in men over 55, it would not be appropriate to place a lower age limit on IRE.

The consultation input varied from agreeing to disagreeing with the proposed comparator. Those that disagreed with the comparator noted that focal therapy can include cryotherapy, HIFU, targeted photodynamic therapy, thermal and microwave ablation, brachytherapy, and SBRT.

A large proportion of consumers providing input commented on the importance of the availability of other services such as counselling for patients with prostate cancer. Consultation input raised the issue of equity of access to IRE stating that people in rural and regional areas may need to go to major population centres for consultation and treatment, and that support for transport, accommodation and carers should be provided.

MBS Item Descriptor and Fee

The consultation input from health professionals and professional organisations mostly agreed with the proposed service descriptor. USANZ stated that the terms “solitary, identifiable tumour on imaging and confirmed on biopsy” should be included to define the population. A health professional commented that IRE is performed under ultrasound guidance in a similar manner to MBS items 37219 and 37220 and so

should include: "... being a service associated with a service to which item 55603 applies". PCFA recommend that an explanatory note accompany the MBS item number to require long consultation with a urologist, and consultation with both a urologist and radiation oncologist, subject to multidisciplinary review, before patients commence treatment.

The consultation input from health professionals and professional organisations ranged from agreeing with the proposed service fee to stating that it should be higher. A health professional noted that a higher rebate may aid patient access due to the cost of disposables for IRE. PCFA stated that consideration should be given to the costs of post-treatment surveillance, such as MRI and biopsy, and the potential requirement for salvage therapies.

PASC noted that RANZCR were not supportive of the application and raised concerns with the difficulty identifying a suitable population, choice of comparator, and lack of data to support the outcomes. PASC also noted that the PCFA were supportive of the application but welcomed additional research.

PASC welcomed input from prostate cancer survivors and consumer groups, who urged funding on the MBS and advocated for equitable access including reduced out of pocket costs.

Next steps

PASC noted the applicant intends to proceed with an Applicant Developed Assessment Report (ADAR).

Applicant Comments on Ratified PICO

Response Regarding Proposed MBS Item and Fee Structure (Table 9 and 10)

1. Treatment Limitation to One per Patient Lifetime
The applicant maintains that up to two treatments should be available. Reducing to one treatment would exclude a small but clinically important group of patients who may require a secondary IRE procedure.

2. Surgical Assistant Fees

The applicant suggests that consideration of surgical assistant fees could be addressed during the future cost modelling stage of the application.

3. Comparator Selection – Active Surveillance (AS)
The applicant does not agree with the selection of Active Surveillance (AS) as a comparator for IRE in patients with Gleason 6 prostate cancer. AS is a non-interventional management strategy and not a therapeutic intervention. In contrast, IRE is a definitive, attempted curative treatment intended for patients with clinically significant prostate cancer. As such, the applicant does not consider AS an appropriate comparator.

4. Proposed Fee Changes (Tables 9 and 10)
The applicant acknowledges and understands the background the committee used to recommend a different MBS code. The applicant wishes to highlight that MBS item 37227 (HDR brachytherapy), also requires additional MBS codes, including 15966.

- MBS 37227 covers the insertion of the delivery device (catheters).
- MBS 15966 covers the insertion of the therapeutic component (implants).

Together, these codes reflect both the procedural and therapeutic components of HDR brachytherapy, with a combined benefit of $644.60 (37227) + $531.95 (15966).

Following this logic, if IRE were to be aligned to 37227 (placement of electrodes), 15966 (administer of therapeutic dose) would also be claimable. This is particularly relevant as, in IRE, the urologist is responsible for both the insertion of the electrodes and the delivery of the therapeutic energy—activities which mirror the dual components of HDR brachytherapy. As such the applicant is comfortable with either the original requested codes, or multiple codes (37227 + 15966) apply for IRE.

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