Australian Government

Department of Health

Application 1686:

^{177}Lutetium Prostate Specific Membrane Antigen (PSMA) imaging and therapy (I&T) for metastatic castrate resistant prostate cancer (mCRPC)

Ratified

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 ^{177}Lu PSMA I&T in patients with metastatic castrate resistant prostate cancer (mCRPC) : PICO Set 1

Component	Description

Population	Patients who have:
	• progressive or symptomatic mCRPC, *AND*
	• have received:
	  ○ *at least one* ASI (abiraterone / enzalutamide / darolutamide via PBS/RPBS), *AND*
	  ○ *at least one* line of chemotherapy (docetaxel +/- cabazitaxel via PBS/RPBS)

Intervention	Diagnostic test 1: PSMA PET/CT *If positive* (SUV_{max} of >15 at ≥1 disease site *AND* SUV_{max} >10 at all measurable sites), proceed to Diagnostic test 2: FDG PET/CT Patients who have: • positive PSMA PET/CT, *AND* • no sites of FDG uptake > PSMA uptake, *AND* • adequate marrow/liver/renal function, are eligible for Therapeutic intervention: • ^{177}Lu PSMA I&T, 7.5-8.5 GBq IVI every 6 weeks for up to 6 cycles • ^{177}Lu PSMA SPECT/CT 24 hours post-infusion
Comparators	Diagnostic tests 1 and 2: no testing with PSMA PET/CT and FDG PET/CT Therapy: • cabazitaxel • standard care if prior cabazitaxel, or unsuitable/unwilling for cabazitaxel
Reference standard	None nominated for PSMA PET/CT or FDG PET/CT
Clinical utility standard	Unclear
Outcomes	***Safety outcomes*** • Radiation exposure (patients, carers, staff) • Adverse reactions to therapy (haematologic, renal, xerostomia, etc) ***Effectiveness outcomes*** *Diagnostic tests:* • Inter- / intra-observer variability • Change in management: proportion of patients excluded from therapy *Therapy outcomes:* • Disease response (tumour marker [PSA], imaging [RECIST, PERCIST]) • Survival (OS, PFS) • Mortality, incl. cancer-specific mortality • QoL ***Economic outcomes*** • Cost-effectiveness (cost per additional quality adjusted life year) ***Healthcare system outcomes***

Component	Description
	• Cost of diagnostic & therapeutic interventions • Cost of additional tests & follow-up required • Total Australian Government health care costs (including cost of treatment received and cost offsets due to tests and treatment avoided).
Assessment questions	• How concordant are the results of the proposed diagnostic tests to the clinical utility standards for both PSMA and FDG PET/CT? Specifically: - What is the effectiveness* of various (if any) PSMA SUV_{max} thresholds for selecting patients for ^{177}Lu PSMA therapy? - What is the effectiveness* & cost-effectiveness of FDG PET/CT for the further selection of patients for ^{177}Lu PSMA therapy? - How does clinical management change as a consequence of PSMA and FDG PET/CT and what proportion of patients are affected? • What is the safety, effectiveness, and cost-effectiveness of ^{177}Lu PSMA-I&T *vs* cabazitaxel *OR* standard care in patients with progressive or symptomatic mCRPC who have failed ≥1 ASI and ≥1 line of taxane-based chemotherapy? Specifically: - What is the evidence to support therapeutic equivalence between ^{177}Lu PSMA I&T and ^{177}Lu PSMA-617 (as the basis to justify applying evidence for ^{177}Lu PSMA-617 in order to request funding for ^{177}Lu PSMA I&T)? - Should ^{177}Lu PSMA and its associated tests be funded by the MBS (the primary question addressed by this PICO)? • What is the effectiveness & cost-effectiveness of post-therapy SPECT/CT for the further management of patients who receive ^{177}Lu PSMA therapy? (* *Safety* of PSMA PET/CT and FDG PET/CT has been accepted by MSAC)

ASI, androgen-receptor signalling inhibitor; CT, X-ray computed tomography; FDG, (fluorine-18)-fluorodeoxyglucose; GBq, gigabecquerel; IVI, intravenous infusion; ^{177}Lu, lutetium-177; MBS, Medicare Benefits Schedule; mCRPC, metastatic castrate-resistant prostate cancer; OS, overall survival; PBS, Pharmaceutical Benefits Schedule; PERCIST, Positron Emission Tomography Response Criteria in Solid Tumors; PET, positron emission tomography; PFS, progression-free survival; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumors; RPBS, Repatriation Pharmaceutical Benefits Schedule; SPECT, single-photon emission computed tomography; SUV_{max}, maximum standardised uptake value

Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of ^{177}Lutetium Prostate Specific Membrane Antigen (PSMA) imaging and therapy (I&T), ^{177}Lu PSMA I&T herein, for metastatic castrate resistant prostate cancer (mCRPC) was received by the Department of Health from a group of academic specialists, co-sponsored by the Australasian Association of Nuclear Medicine Specialists (AANMS).

The application (p2) explains that to date, all prospective trials have been undertaken using ^{177}Lu PSMA-617 which is under patent with Novartis, who have no plans to apply for registration in Australia. The application further explains that ^{177}Lu PSMA-617 and ^{177}Lu PSMA I&T are almost identical peptides with equivalent clinical responses and toxicities. Good laboratory practice (GLP) produced ^{177}Lu PSMA I&T is currently being offered around Australia under the Special Access Scheme (SAS) and is approved by Department of Veteran's Affairs (DVA) for veterans. There is no available formal funding, leading to inequitable access to treatment in this effective class of drugs for patients suffering from a painful lethal condition.

The MSAC Executive noted that ^{177}Lu PSMA I&T is produced under GLP (good laboratory practice), is currently being offered around Australia under the TGA's Special Access Scheme and is approved by DVA for veterans. Based on the evidence submitted by the applicant, and with regard to both dose and product affinity for the intended receptor, the MSAC Executive agreed that the non-pharma supported (feasible) off-patent ^{177}Lu PSMA I&T is bioequivalent in clinical responses and toxicities to the un-available well-validated ^{177}Lu PSMA-617 for the treatment of [patients] with mCRPC, and so the evidence base for ^{177}Lu PSMA-617 could be applied to assess the clinical performance of ^{177}Lu PSMA I&T.

Thus, for the purposes of this PICO confirmation (and in the subsequent assessment report), the evidence base that is available for ^{177}Lu PSMA-617 is assumed to apply to ^{177}Lu PSMA I&T.

The clinical claim made by the applicant is that the use of the ^{177}Lu PSMA I&T results in superior health outcomes compared to the cabazitaxel and standard care. No claims regarding comparative safety were provided.

Although the application detailed a request for the use of ^{177}Lu PSMA I&T, only for the treatment of mCRPC, through discussions with the applicant, it became evident that requests for prior testing to select patients for treatment was required. Thus, the application is for two diagnostic tests (both positron emission tomography (PET)/computerised tomography (CT)) and one therapeutic intervention with post-treatment imaging.

Although not specifying a clinical claim for the codependent technology, expanding to include the diagnostic pre-requisite tests is presumed to not change the clinical claim for the therapy.

PICO criteria

Population

Metastatic castrate refractory prostate cancer is a disease that resulted in the deaths of over 3000 patients in Australia in 2020. The natural history of prostate cancer varies with its presentation and features. Some patients present with *de novo* metastatic disease (known as mHSPC – metastatic hormone sensitive prostate cancer). The application states these patients compromise about 10% of all the initial presentations of prostate cancer annually. These patients are usually treated with androgen deprivation therapy (ADT) that remove physiological testosterone from their body to control their cancer, before considering the need for further therapies such as high potency testosterone antagonists/synthesis inhibitors such as enzalutamide/abiraterone or the consideration of chemotherapy (docetaxel, cabazitaxel) used as needed as the disease progresses. Recent data from large studies in this mHSPC population suggests that median OS in this population exceeds 4 years.

The majority of patients with mCRPC are those who have had their primary prostate cancer previously treated (either by surgery or radiation therapy, or both) and who have had prostate serum antigen (PSA) relapse and the development of metastases. These patients will thereafter be treated with ADT, with its ensuing side-effects relating to testosterone depletion (hot flashes, loss of bone/muscle mass, loss of libido, increased risk of dementia) and thereafter a combination of agents as above over a course of 3-7 years of treatment on average (5 year survival is poor).

Aside from the morbidity associated with mCRPC, with is the lethal disease state, there is also significant morbidity associated with treatment-refractory disease exacerbated by the bone-tropic pattern of spread in the cancer as it progresses. Generally, approximately 30% of patients with prostate cancer require the use of opioid analgesia during the course of their disease for metastases. Skeletal-related events (SREs) have clinically meaningful and significant impact on health-related QOL, with physical, emotional, and functional wellbeing all declining after pathologic fractures and radiation therapy.

As noted above, the application is making a request for MBS listing of two pre-requisite PET/CT scans to determine eligibility for the therapeutic intervention with post-treatment imaging. The population thus, changes through the diagnostic process as follows:

Diagnostic Test 1 Whole body prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/computed tomography (CT) - PSMA PET/CT: Patients who have progressive or symptomatic mCRPC who have received at least one androgen receptor signalling inhibitor (ASI; abiraterone/enzalutamide/darolutamide via PBS/RPBS) as well as at least one line of chemotherapy (docetaxel +/- cabazitaxel via PBS/RPBS) in the setting of mCRPC. Darolutamide was considered by the PBAC for patients with non-metastatic castrate resistant prostate cancer at high risk of distant metastases (March 2021, July 2020). The applicant anticipates darolutamide to be PBS listed metastatic disease status agnostic.

Diagnostic Test 2 Whole body ^{18}F-fluorodeoxyglucose (FDG) PET/CT – FDG PET/CT: Patients who have progressive or symptomatic metastatic castrate resistant prostate cancer (mCRPC) who have received at least one androgen receptor signalling inhibitor (ASI; abiraterone/enzalutamide/darolutamide via PBS/RPBS) as well as at least one line of chemotherapy (docetaxel +/- cabazitaxel via PBS/RPBS) in the setting of mCRPC **AND** who are PSMA-positive (according to PSMA PET/CT; defined as maximum

standardised uptake value [SUV_{max}] of >15 at a single site of disease and SUV_{max} >10 at all sites of measurable disease).

Therapeutic intervention ^{177}Lutetium prostate-specific membrane antigen imaging and therapy (^{177}Lu PSMA I&T): Patients who have progressive or symptomatic metastatic castrate resistant prostate cancer (mCRPC) who have received at least one androgen receptor signalling inhibitor (ASI; abiraterone/enzalutamide/darolutamide via PBS/RPBS) as well as at least one line of chemotherapy (docetaxel +/- cabazitaxel via PBS/RPBS) in the setting of mCRPC **AND** who are PSMA-positive by PSMA PET/CT with NO FDG discordant disease.

The proposed population is:

- consistent with those enrolled in the TheraP trial (a comparison of ^{177}Lu PSMA-617 and cabazitaxel in patients with PSMA-positive mCRPC and no sites of metastatic disease with discordant FDG-positive and PSMA-negative findings; Hofman 2021); and
- similar to those enrolled in the VISION trial (a comparison of ^{177}Lu PSMA-617 + standard care versus standard care alone in patients with PSMA-positive mCRPC; Sartor 2021).

PASC noted that 'progressive' or 'symptomatic' mCRPC were not defined in the PICO. Progressive disease was defined differently across the pivotal trials:

- *TheraP (NCT03392428)[1]: rising prostate specific antigen (PSA) on three consecutive measurements, and PSA ≥20 ng/mL.*
- *VISION (NCT03511664)[2]: based on at least one of the following criteria*
  - *Serum/plasma PSA progression defined as two consecutive increases in PSA over a previous reference value measured at least 1 week prior. The minimal start value is 2.0 ng/mL*
  - *Soft tissue progression defined as an increase ≥20% in the sum of the diameter (SOD) (short axis for nodal lesions and long axis for non nodal lesions) of all target lesions based on the smallest SOD since treatment started or the appearance of one or more new lesions*
  - *Progression of bone disease: evaluable disease or new bone lesions(s) by bone scan.*

PASC advised that 'progressive' and 'symptomatic' mCRPC needed to be defined.

PASC also noted that adequate organ function (renal, bone marrow, liver function) was an eligibility criterion across both pivotal trials.

PASC noted that patient suitability for the intervention would be assessed by a multidisciplinary team (MDT). This needed to be reflected in the PICO.

The application estimated that 500 patients would be treated with ^{177}Lu PSMA I&T per year. In discussion, the applicant considered that this was a likely overestimate when accounting for those who undergo treatment with docetaxel. The application also stated (p27) that '[d]emand would be expected to increase by 10-15% per year until it reaches capacity, which would be 60% of the [patients] who die from metastatic prostate cancer each year (1800 [patients] per year)'. The applicant considered that capacity would never be reached.

[1] https://clinicaltrials.gov/ct2/show/NCT03392428
[2] https://clinicaltrials.gov/ct2/show/NCT03511664

PASC advised that issues affecting utilisation (access, procedure complexity [for both patients and providers]) and likely capacity constraints should be addressed in the assessment report.

Intervention

The application is for two diagnostic tests (both positron emission tomography (PET)/computerised tomography (CT)) and one therapeutic intervention with post-treatment imaging (i.e., codependent technologies).

PASC noted that the intervention consisted of four codependent elements – diagnostic imaging tests (two), radioligand therapy and post-treatment imaging.

The application notes (p20) that referrals for ^{177}Lu PSMA I&T will come from medical oncologists, radiation oncologist or oncologic surgeons, with the procedure undertaken by appropriately licenced nuclear medicine specialists.

Positron emission tomography (PET)/computerised tomography (CT)

PET imaging measures the biodistribution of an intravenously injected biological tracer labelled with a positron-emitting radionuclide (Scott 2001), detecting, and quantifying biological processes occurring within the body.

The MSAC 1632 PSD (July 2021) stated (p5) that the [MSAC 1632] Ratified PICO noted that PET imaging is now almost always combined with CT, with scans collected using a single, hybrid PET/CT scanner ([MSAC 1632] PICO Confirmation, p14). There are several hybrid PET/CT devices listed on the Australian Register of Therapeutic Goods (ARTG) (ARTG numbers: 343270, 324191, 296394, 292543, 271560, 144218 and 118077).

Diagnostic Test 1:
Whole body prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/computerised tomography (CT) – PSMA PET/CT

Prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/computerised tomography (CT), PSMA PET/CT herein, was recently considered by MSAC (MSAC 1632, July 2021). The PET/CT scan requested in the current application is understood to be the same as that considered in MSAC 1632, however the population under consideration in this application is not eligible for the test considered and ultimately supported by MSAC (MSAC 1632 Public Summary Document [PSD], July 2021).

The MSAC 1632 PSD (July 2021) described PSMA PET/CT (p7) as a non-invasive imaging procedure that involves the administration of one of several radiopharmaceutical tracers that share the characteristic of highly specific binding to PSMA. PET imaging measures the biodistribution of an intravenously injected biological tracer labelled with a positron-emitting radionuclide. In this way, PET imaging can detect and quantify a biological process occurring within the body. The most widely used radiopharmaceutical tracer in clinical practice in Australia is ^{68}Ga [gallium-68]-PSMA-11. Radiopharmaceuticals such as ^{68}Ga-PSMA-11, that are produced extemporaneously in a facility holding a GMP license (license to manufacture therapeutic goods), are exempt from a requirement for ARTG listing under Schedule 5(6) and 8(2) of the Therapeutic Goods Regulations 1990 and part 3-3 of the Therapeutic Goods Act 1989 (p5 MSAC 1362 PSD, July 2021). The proposed service included PET in combination with CT.

The applicant stated that when using beta emitter therapy such as Lutetium, there needs to be a minimum number of decays within the cell in order to translate single stranded DNA breaks across to double stranded DNA breaks. This roughly translates to the intensity of a tumour deposit on a PSMA PET/CT scan.

The applicant noted that two randomised trials (Hofman 2021 [TheraP]; Sartor 2021 [VISION]) assessing ^{177}Lu PSMA-617 for mCRPC utilised PSMA PET/CT scans to assess patient eligibility for treatment with ^{177}Lu PSMA for mCRPC. Both trials required that patients had PSMA-positive mCRPC, determined with the use of gallium-68 (^{68}Ga)–labelled PSMA-11 (^{68}Ga-PSMA-11) PET/CT imaging at baseline. PSMA-positive was defined differently in the trials:

- disease with a maximum standardised uptake value (SUV_{max}) of at least 20 at a site of disease and greater than 10 at all other measurable sites of metastatic disease, and no sites of metastatic disease with discordant 2-[^{18}F]FDG-positive (see below) and PSMA-negative findings (Hofman 2021); and
- ^{68}Ga-PSMA-11 uptake greater than that of liver parenchyma in one or more metastatic lesions of any size in any organ system (Sartor 2021).

The applicant indicated that the PSMA PET/CT scan identifies if the PSMA target is present for treatment and if the PSMA target is expressed adequately to gain a good treatment response. Emmett (2019) reported the results of a prospective pilot trial that enrolled patients with mCRPC previously treated with either abiraterone or enzalutamide, and had failed, refused, or been ineligible for taxane-based chemotherapy. Further eligibility criteria for the trial included uptake on PSMA PET above or equal to liver activity, with no ^{18}F-Fluoroedeoxyglucose (FDG) PET-discordant disease. Patients were treated with ^{177}Lu PSMA-617 for four cycles. In their assessment of predictors of treatment response, the authors reported that both PSMA SUV_{max} and SUV_{mean} at screening were predictive of a ≥30% reduction in PSA with ^{177}Lu PSMA-617 therapy; SUV_{max} of 17 ± 9 and 44 ± 15 in those without and in those with response, respectively (P <0.007). PSMA SUV_{mean} was 6 ± 4 and 10 ± 4 in those without and in those with response, respectively (P <0.04). Emmett (2019) also reported that no patient enrolled with an SUV_{max} <15 on PSMA PET had a biochemical treatment response to ^{177}Lu PSMA-617. This is in contrast to the eligibility criteria in the TheraP trial (Hofman 2021) requiring a SUV_{max} of at least 20. The application noted (p19) that over 80% of patients in this clinical stage have disease 'deemed suitable for ^{177}Lu PSMA I&T on PSMA PET/CT imaging.

PASC stated that the proposed PSMA PET/CT SUV_{max} thresholds should be justified (see "Comparator" below) . Additionally, standardisation of PET instrumentation and diagnostic PSMA ligand use to ensure consistent measurement of SUV_{max} should be addressed.

Diagnostic Test 2:

Whole body ^{18}F-fluorodeoxyglucose (FDG) PET/CT – FDG PET/CT

^{18}F-fluorodeoxyglucose (FDG) is a radioactive simple sugar most commonly used in PET/CT scans. The sugar accumulates in, and thus allows for detection of, metabolically active malignant lesions. FDG PET/CT is a pivotal modality for cancer imaging, assisting diagnosis, staging of patients with newly diagnosed malignancy, restaging following therapy and surveillance (Hofman & Hicks 2016).

The applicant explained that following assessment of PSMA target presence and levels (via PSMA PET/CT), the FDG PET/CT scan then confirms that there are no sites of metastatic disease with no PSMA target at all – these sites will not respond to targeted PSMA therapy, thus for these patients, other systemic options

would be preferable. As noted above, the TheraP trial (Hofman 2021) included FDG PET/CT in the imaging criteria (i.e., more stringent criteria) to determine patient eligibility for enrolment in the trial.

PASC noted that although FDG PET/CT was *used to assess eligibility for the TheraP trial (Hofman 2021), it was not used for assessment of eligibility in the VISION trial (Sartor 2021). While acknowledging that there may be evidence that lesions which showed greater FDG than PSMA avidity were associated with a poorer prognosis, PASC noted that there was no direct evidence that such "PSMA/FDG discordance" (as opposed to outright PSMA negativity) should preclude ^{177}Lu PSMA therapy, and that the additional requirement for FDG PET/CT added cost and complexity to the proposed intervention. PASC stated that the requirement for FDG PET/CT should be justified in the assessment report.*

FDG PET/CT is currently available on the MBS for whole body scans or scans of the brain only, see Table 4 in the attachment. Notably, the MBS item descriptors do not specify the radionuclide and the fee for whole body FDG PET ranges from $953.00 to $999.00, with an additional fee of $100 for an associated non-contrast CT scan (MBS item 61505).

The applicant anticipated that the results of the PSMA PET/CT scan would be available prior to proceeding to the FDG PET/CT scan. The applicant also stated that the PSMA and FDG PET/CT scans could not be undertaken on the same day. Access to PSMA PET/CT imaging is limited by the number of PET/CT equipped sites. As of 09 November 2021, 92 sites were listed on the Department of Health's website (Australian Government Department of Health 2021). Notably, most PET scanners are in major cities, therefore uptake of PSMA and FDG PET/CT among patients in rural or remote areas may be restricted. The requirement for two PET/CT scans on different days may further restrict uptake among patients in rural or remote areas.

Therapeutic intervention:

^{177}Lutetium prostate-specific membrane antigen imaging and therapy (^{177}Lu PSMA I&T)

The application states (p2) that PSMA targeted radionuclide therapy is an emerging new class of therapy for the treatment of mCRPC. The treatment is a targeted intravenous radiotherapy which enters the cancer cell via the PSMA receptor. The PSMA receptor is overexpressed in prostate cancer, with expression increasing in metastatic and castrate resistant disease.

^{177}Lu PSMA I&T is a targeted radionuclide therapy that is administered within accredited nuclear medicine departments as an outpatient service. It involves an intravenous injection and there is no specific preparation on behalf of the patient.

An oncology specialist will identify a patient with progressive metastatic prostate cancer as one who will benefit from, and be appropriate for, ^{177}Lu PSMA I&T.

Screening with PSMA PET/CT and FDG PET /CT will determine if the patient has an adequate level of PSMA 'target' at all sites of measurable disease such that they will be expected to derive significant benefit from the treatment. The application (p19) considers that currently, those who are expected to benefit have an SUV_{max} >15 at a single site and >10 at all sites of measurable disease on the PSMA PET scan with no sites of FDG discordance. The SUV_{max} >15 threshold is supported by data presented in Emmett (2019), see above.

Other requirements (assessed on blood test) include platelets >75 x 10^9/L and rising, haemoglobin (Hb) >80 g/L and estimated glomerular filtration rate (eGFR) >40 mL/minute/1.73m^2 body surface area.

Once a patient has been identified as appropriate for ^{177}Lu PSMA I&T based on both PET imaging characteristics, stage in the patient journey (failure of at least one taxane-based chemotherapy and one ASI), and haematologic and biochemical results (appropriateness will be decided by a theranostics specialist) – a dose of ^{177}Lu PSMA I&T is booked. The application states that it takes approximately 2 weeks for the Lutetium be ordered, delivered, and labelled chemically to PSMA I&T (must be done within an accredited radiochemistry facility).

The procedure itself takes some hours in an outpatient setting in an accredited nuclear medicine facility. A cannula is placed in a vein, and the ^{177}Lu PSMA I&T is administered as a slow intravenous injection. The dose per cycle is currently set at between 7.5-8.5 gigabecquerel (GBq) Lu PSMA intravenously – although recent dose escalation phase 1 trials have found no dose limiting toxicity at significantly higher doses. Previous dose calculations have been set based on estimated delivered radiation dose to non-target organs such as the kidney and salivary glands. However, these dose calculations were undertaken using external beam set limits and it is likely that these calculations have been overestimating dose estimates to non-target organs. It is possible that the radiation dose per injection will be increased in patients with higher volume disease in the future. An oral dose of 8mg dexamethasone may also be administered at the time of injection to minimise the chance of nausea or transient increase in pain. Although the application stated that 8mg of dexamethasone is administered, the applicant clarified that this does not need to be mandatory, it could be based on clinical need (high volume bone disease, baseline nausea).

The patient will stay isolated in the nuclear medicine facility, encouraged to drink water, until radiation levels reduce to the safe government limit for discharge (25uSv /hour at one metre).

PASC noted that ^{177}Lu PSMA required vigorous hydration and frequent voiding to reduce radiation dose to the urinary tract as the compound is excreted by the kidneys and nephrotoxicity is a potential adverse effect. Although the application noted this could be achieved with oral hydration, PASC noted that intravenous (IV) hydration may be required. PASC also noted that PSMA is concentrated in the salivary glands and xerostomia (dry mouth) may be an adverse effect. Irradiation of haemopoietic bone marrow, particularly in patients with a high skeletal metastatic burden, may result in haematologic toxicity (cytopaenias).

The patient is given full radiation safety education on limiting radiation dose to the public, family, and caregivers. Radiation safety guidelines are developed with theranostics physicists according to the Australasian Association of Nuclear Medicine Specialists (AANMS) Theranostics position statement.

Imaging (^{177}Lu PSMA single-photon emission computed tomography (SPECT)/CT) involving a whole-body scan is acquired 24 hours following injection to confirm uptake at tumour sites, and to allow serial imaging quantitation of treatment response.

PASC also noted that although SPECT/CT following ^{177}Lu PSMA therapy was conducted in the TheraP trial (Hofman 2021), it was not in the VISION trial (Sartor 2021). PASC stated that the requirement for SPECT/CT following ^{177}Lu PSMA therapy and its impact on subsequent management should be justified in the assessment report.

Repeat doses of ^{177}Lu PSMA I&T occur at 6 weekly intervals for an average of 6 doses – until the patient is no longer clinically benefiting or they do not have significant persistent disease to target with ^{177}Lu PSMA I&T.

PASC indicated that criteria for continuing/ceasing ^{177}Lu PSMA treatment should be clarified.

On cessation of ^{177}Lu PSMA I&T, after the patient is no longer clinically benefiting, the patient's oncology specialist will determine the next appropriate treatment options based on disease volume and phenotype, patient age, co-morbidities, and patient informed decision.

The application noted that production of ^{177}Lu PSMA I&T is currently through the TGA exemption for production of radiopharmaceuticals in public or private hospitals for local use and not for on-sale. A network of academic theranostics departments across Australia have undergone accreditation for production of GLP compliant Lu PSMA for trial purposes. Both treatment and imaging radiopharmaceuticals are produced across Australia with this method of production:

1. Ga PSMA – MSAC approved for GLP compliant production.
2. Ga DOTATATE – MSAC approved for GLP compliant production.
3. 177 Lutetium DOTA – multiple approvals for funding using state processes across Australia.
4. 177 Lutetium PSMA 617 – all production across Australia for multiple trials using GLP compliant production methods.
5. 177 Lutetium PSMA I&T – produced for patient doses across Australia under the SAS scheme.
6. GLP compliant production for clinical purposes is a TGA acknowledged process that has been used extensively for the benefit of the patients in theranostics. This is a radiation procedure with trained radiochemists undertaking the labelling and safety demonstrated across hundreds of thousands of doses across the theranostics space in the last 20 years.
7. There is no GMP compliant alternative – and given the safety demonstrated consistently across high level trials and in clinical practice – the argument for delaying treatment availability to enforce a commercial solution goes against the TGA exemption (which reflects the theranostics space), the safety already demonstrated with the current system, and the urgent clinical needs of the patients involved.

The application noted that GLP compliant production is routinely used in nuclear medicine departments for radio-pharmacy production across Australia and has been a safe, cost effective, highly accessible model for production of radiopharmaceuticals. It is proposed that the production of ^{177}Lu PSMA I&T be continued along this model of production.

Comparator(s)

No comparators were nominated for PSMA PET/CT, FDG PET/CT or SPECT/CT.

PASC nominated the following additional comparisons to include in the assessment report to justify the nominated threshold for PSMA PET/CT positive status indicating eligibility for 177Lu PSMA therapy and to justify the requirement for FDG PET/CT and post-treatment SPECT/CT:

Component	***Comparison***
PSMA PET/CT SUV_{max} >15 at a single site of disease and SUV_{max}	• *PSMA PET/CT SUV_{max} >20 at a single site of disease and SUV_{max} >10 at all sites of measurable disease (as per the TheraP trial)*

>10 at all sites of measurable disease	• *PSMA uptake in ≥1 metastatic lesion > in liver (as per the VISION trial)*
FDG PET/CT	*No FDG PET/CT (as per the VISION trial)*
Post-treatment SPECT/CT	*No post-treatment SPECT/CT (as per the VISION trial)*

PASC noted that these SUV_{max} thresholds were derived from clinical trials using ^{68}Ga-PSMA-11, with harmonisation of PET instrumentation among clinical trial sites, and questioned whether all other diagnostic PSMA ligands would be expected to produce identical SUV_{max} values on all other PET instruments.

PASC stressed that the assessment report should justify the requirement for FDG PET/CT in the proposed management pathway by presenting three comparisons (see also "Outcomes" below):

- *the proposed management algorithm of codependent interventions with FDG-PET/CT (*Figure 3*) against the current management algorithm (*Figure 2*);*
- *the possible management algorithm of codependent interventions without FDG-PET/CT (*Figure 4*) against the current management algorithm (*Figure 2*); and*
- *the proposed management algorithm with FDG-PET/CT (*Figure 3*) against the possible management algorithm without FDG-PET/CT (*Figure 4*).*

Similarly, PASC stressed that the assessment report should justify the requirement for post-treatment SPECT/CT in the proposed treatment pathway, including by estimating the patient outcomes and consequences for the subsequent provision of healthcare resource of not including this use.

The application reasonably nominated cabazitaxel as a comparator for ^{177}Lu PSMA I&T. The PBS restriction for cabazitaxel (see Table 5 in the attachment) specifies that use of cabazitaxel is restricted to patients with mCRPC who have failed treatment with docetaxel due to resistance or intolerance. Although the eligibility criteria for cabazitaxel does not require failure of ASIs, it may be reasonable to assume that oral therapies such as abiraterone or enzalutamide would be used prior to a further course of chemotherapy. For some patients, cabazitaxel will be displaced rather than replaced. The TheraP trial provides a comparison of ^{177}Lu PSMA-617 versus cabazitaxel. *PASC accepted that cabazitaxel may be displaced rather than replaced in a proportion of patients and indicated that this proportion be clarified in the assessment report; the relevant comparator for this group would be standard care.*

In further discussions with the applicant, it became apparent that standard care, for those who had been treated with cabazitaxel and for those unable or unwilling to be treated with cabazitaxel, would also be a relevant comparator. *Similarly, while acknowledging that a small proportion of patients would be chemotherapy ineligible due to age or comorbidities, this proportion should be clarified in the assessment report.* The VISION trial (Sartor 2021) provided a comparison of ^{177}Lu PSMA-617 + standard care versus standard care alone. The standard care therapies taken by patients in that trial are presented in Table 2. Notably, patients in the VISION trial were able to continue treatment with ASIs while on treatment with ^{177}Lu PSMA-617. The PBS restrictions for abiraterone and enzalutamide (see Table 5 in the attachment) specify that treatment must cease 'if progressive disease develops while on [treatment]', thus treatment with ASI should cease (agreed to by the applicant) upon initiating treatment with ^{177}Lu PSMA I&T.

Table 2 Standard care therapies taken by patients in the VISION trial

Treatment	^{177}Lu PSMA-617 + standard care N=529	Standard care alone N=205	Overall N=734
Medication, n (%)	529 (100)	205 (100)	734 (100)
Radiotherapy, n (%)	79 (14.9)	34 (16.6)	113 (15.4)
Other interventions, n (%)	24 (4.5)	5 (2.4)	29 (4.0)
Standard care anti-cancer medications[a] received by ≥1% of patients, n (%)[b]			
Gonadotropin-releasing hormone analogues	468 (88.5)	172 (83.9)	640 (87.2)
Glucocorticoids	335 (63.3)	134 (65.4)	469 (63.9)
Androgen receptor pathway inhibitors Enzalutamide Abiraterone Apalutamide Darolutamide	278 (52.6) 157 (29.7) 132 (25.0) 10 (1.9) 2 (0.4)	139 (67.8) 87 (42.4) 72 (35.1) 1 (0.5) 1 (0.5)	417 (56.8) 244 (33.2) 204 (27.8) 11 (1.5) 3 (0.4)
Denosumab	184 (34.8)	80 (39.0)	264 (36.0)
Bisphosphonates	45 (8.5)	28 (13.7)	73 (9.9)
Testosterone 5α reductase inhibitors	16 (3.0)	11 (5.4)	27 (3.7)
Degarelix acetate Degarelix	12 (2.3) 6 (1.1)	1 (0.5) 5 (2.4)	13 (1.8) 11 (1.5)
Oestrogens	12 (2.3)	1 (0.5)	13 (1.8)

Source: Table S9, p24 of the Supplementary Appendix to Sartor (2021)

[a+] Standard-of-care supportive measures not shown, e.g. pain control, fluid hydration, etc.

[b] Overall; ranked by overall frequency; coded using WHO Drug Global version March 2020 B3, except for androgen receptor pathway inhibitors, which includes the drugs shown from the codes 'anti-androgens' and 'other hormone antagonists and related agents'.

Olaparib was suggested to be a relevant near market comparator among the sub-group of patients with mCRPC who have BRCA1/BRCA2 pathogenic gene variants based on recent MSAC and PBAC considerations (MSAC 1618 PSD, April 2021 MSAC meeting; Olaparib PSD, March 2021 PBAC meeting). *PASC agreed with the applicant that olaparib was not a relevant comparator.*

Reference standard (for investigative technologies only)

No reference standards were nominated for PSMA PET/CT or FDG PET/CT, nor are any apparent.

PASC agreed that, in the absence of a reference standard, the analytical comparison should be "concordance between the test and a clinical utility standard should be presented as overall, positive, and negative percent agreement and/or as a Cohen's kappa coefficient measure of agreement" (as per the MSAC Guidelines).

Clinical utility standard (for codependent investigative technologies only)

PSMA PET/CT

The clinical utility standard for PSMA PET/CT in both the TheraP and VISION trials was ^{68}Ga-PSMA-11 PET/CT imaging, with TheraP (Hofman 2021) also requiring disease with a SUV_{max} of ≥20 at a site of disease and >10 at all other measurable sites of metastatic disease.

The requested MBS item descriptor for PSMA PET/CT is radionuclide agnostic and eligibility for FDG PET/CT requires a SUV_{max} of >15 at a single site of disease and SUV_{max} >10 at all sites of measurable disease. The MSAC 1632 PSD (July 2021) states that ^{68}Ga-PSMA-11 is the most widely used radiopharmaceutical tracer in clinical practice in Australia. Thus, the proposed testing for PSMA-positive mCRPC is likely to align with the clinical utility standard, although the possible implications of the different requirements for SUV_{max} should be addressed.

PASC considered that the clinical utility standard for PSMA PET/CT was unclear based on different PSMA criteria being applied in the TheraP and VISION trials. PASC noted that although MSAC accepted that all available diagnostic PSMA agents may be equivalent (MSAC 1632 PSD), it is not established that all will give the same lesional SUV_{max} values as required in the PICO. PASC also noted that SUV can vary dependent on the camera and software used. The assessment report for this application will need to provide analytical concordance data across diagnostic PSMA ligand options available in Australia against the different PSMA criteria as proposed in the item descriptor and as defined in the trials.

FDG PET/CT

The clinical utility standard for FDG PET/CT in the TheraP trial was 2-flourine-18 [^{18}F] fluoro-2-deoxy-D-gluycose (FDG) PET/CT. This is consistent with the requested MBS item descriptor for FDG PET/CT, although the item descriptor includes a time limit (to be conducted within 60 days of the PSMA PET/CT), which was not specified in the TheraP trial publication (Hofman 2021). Should this differ, an evaluation of the implications in differences in timing would need to be assessed.

The VISION trial (Sartor 2021) did not include FDG PET/CT, which was noted by the authors to be a possible advantage as patients were eligible for inclusion in the trial based on only one PET/CT scan. The implications of the lack of FDG PET/CT in this trial and its subsequent impact on the results would need to be addressed, including assessing the applicability of the VISION trial results to the intended Australian population.

Outcomes

Safety outcomes

- Radiation exposure (patients, nuclear medicine technologists, nurses).
- Adverse effects of the radiopharmaceuticals, including bone marrow and renal toxicity.

Effectiveness outcomes

Diagnostic accuracy

No outcomes for the two diagnostic tests, PSMA PET/CT or FDG PET/CT, were nominated. In the absence of relevant comparators and reference standards, standard effectiveness outcomes assessing the diagnostic accuracy of the tests (sensitivity, specificity, positive and negative predictive values, area under the curve (AUC) of the receiver operating characteristic (ROC) curve) are not relevant.

Other characteristics such as intra- and inter-observer variability in reading the PET/CT scans would be relevant.

Change in management

The purpose of the PSMA and FDG PET/CT scans is to assess eligibility for treatment with ^{177}Lu PSMA I&T. Thus, a result below or above a nominated threshold would mean that patients were not eligible and eligible for treatment with ^{177}Lu PSMA I&T, respectively.

Relevant outcomes would be the proportion of patients who meet the nominated thresholds for PSMA PET/CT and the proportion of those who proceed to FDG PET/CT who do not have a PSMA and FDG PET/CT discordance. The applicant suggested that the combination of PSMA and FDG PET/CT reduces the number of patients eligible for treatment to approximately 75% of patients (25% will not have suitable disease). Hofman (2021) reported that 28% of patients who were screened for enrolment in the TheraP trial did not meet the eligibility criteria, primarily due to discordant results from PSMA PET/CT and FDG PET/CT.

Oncologic and patient outcomes

The outcomes nominated in the application include:

1. Progression free survival/treatment response.
2. Key quality of life indicators.
3. Pain score improvement.
4. Patient related outcomes measuring improved quality of life parameters.
5. Bioequivalence for ^{177}Lu PSMA I&T and ^{177}Lu PSMA-617.

Each of these outcomes are appropriate, however overall survival would be an additional relevant outcome.

PASC indicated that disease response (tumour marker (PSA [prostate-specific antigen]), imaging (RECIST [Response Evaluation Criteria in Solid Tumours], PERCIST [Positron Emission Tomography Response Criteria in Solid Tumors]) should be included as a 'Therapy outcome'.

PASC indicated that cost of additional tests and additional follow-up should be included as a 'Healthcare system outcome'.

PASC acknowledged the MSAC Executive's determination that ^{177}Lu PSMA I&T was "bioequivalent in clinical responses and toxicities" to ^{177}Lu PSMA-617. However, PASC considered that the assessment report should assess the equivalence or non-inferiority of the two as:

- *The only evidence of "bioequivalence" provided by the applicant is from one small, single centre, retrospective narrative review - a comparative intrapatient (i.e., for different PRLT [PSMA-targeted radioligand therapy] courses) and interpatient dosimetry analysis was performed for ^{177}Lu PSMA I&T and ^{177}Lu PSMA-617" (Kulkarni 2016);*
- *There are no published RCTs of ^{177}Lu PSMA I&T in mCRPC; two ongoing RCTs in mCRPC were found on Clinicaltrials.gov (NCT04188587, NCT04647526) & ECLIPSE RCT (proposed by Curium [France], not yet registered);*
- *The most recent meta-analysis (Sadaghiani 2021) includes only 2/24 studies of ^{177}Lu PSMA I&T, both retrospective;*

- *Four ongoing Australian multicentre RCTs (PRINCE [NCT03658447], LuPARP [NCT03874884], ENZA p [NCT04419402], UpFrontPSMA [NCT04343885]) are all using "un-available well validated ^{177}Lu PSMA-617".*

The applicant stated at PASC that the predominant use of ^{177}Lu PSMA-617 in published trials is due to current trial funding arrangements, and that the number of trials using ^{177}Lu PSMA I&T is expected to increase in the near future.

PASC suggested that the following questions be addressed:

- *What is the evidence to support therapeutic equivalence between ^{177}Lu PSMA I&T and ^{177}Lu PSMA-617 (as the basis to justify applying evidence for ^{177}Lu PSMA-617 in order to request funding for ^{177}Lu PSMA I&T)?*
- *Should ^{177}Lu PSMA and its associated tests be funded by the MBS (the primary question addressed by this PICO)?*

*PASC also requested that the assessment report provide a comparison of a proposal where FDG PET/CT is included (*Figure 3*) and a proposal where it is not (*Figure 4*). This is not only to address the proportion of patients who would be deemed ineligible (in the situation where FDG PET/CT is included), but also the consequences for patient outcomes.*

Assessment framework (for investigative technologies)

No trials were identified that compared the efficacy of ^{177}Lu PSMA I&T in those who were:

(i) PSMA PET/CT-positive with no FDG PET/CT discordance;
(ii) PSMA PET/CT-positive with FDG PET/CT discordance;
(iii) PSMA PET/CT-negative with no FDG PET/CT discordance; and
(iv) PSMA PET/CT-negative with FDG PET/CT discordance.

Thus, a linked evidence approach will likely be required to establish the proposed requirement for a (i) minimum PSMA-positive threshold (defined as SUV_{max} >15 at a single site of disease and SUV_{max} >10 at all sites of measurable disease) and (ii) no PSMA/FDG discordance, and the implications of these characteristics on intermediate and health outcomes as a results of treatment with ^{177}Lu PSMA I&T, see Figure 1.

PASC considered that a linked evidence approach would be required, including to establish the minimum PSMA-positive threshold and the consequences for patients of PSMA/FDG discordance.

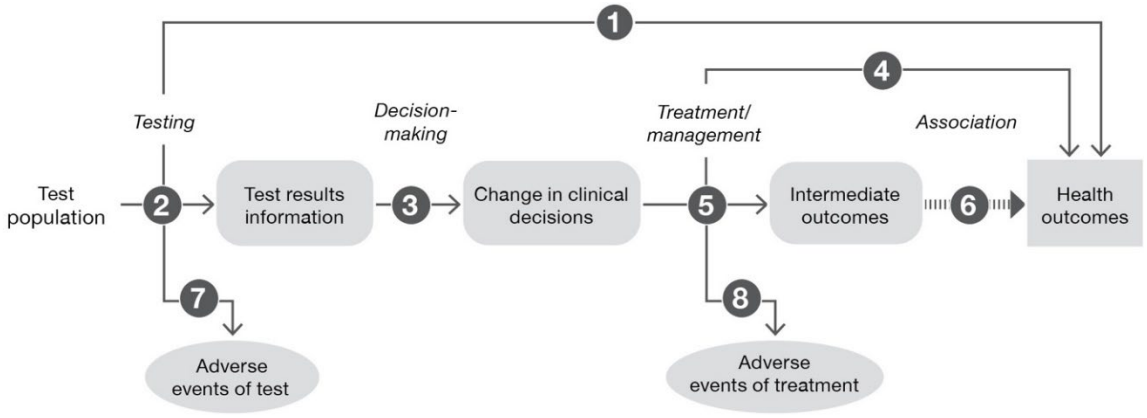

Figure 1 Generic assessment framework showing the links from the test population to health outcomes

Figure notes: 1: direct from test to health outcomes evidence; 2: test accuracy; 3: change in diagnosis/treatment/management; 4: influence of the change in management on health outcomes; 5: influence of the change in management on intermediate outcomes; 6: association of intermediate outcomes with health outcomes; 7: adverse events due to testing; 8: adverse events due to treatment

Clinical management algorithms

The current and proposed clinical management algorithms presented in the application are presented in Figure 5 in the attachment. The applicant subsequently provided an updated proposed algorithm, see Figure 6 in the attachment. The following current (Figure 2) and proposed (Figure 3) clinical management algorithms were developed during the writing of this PICO.

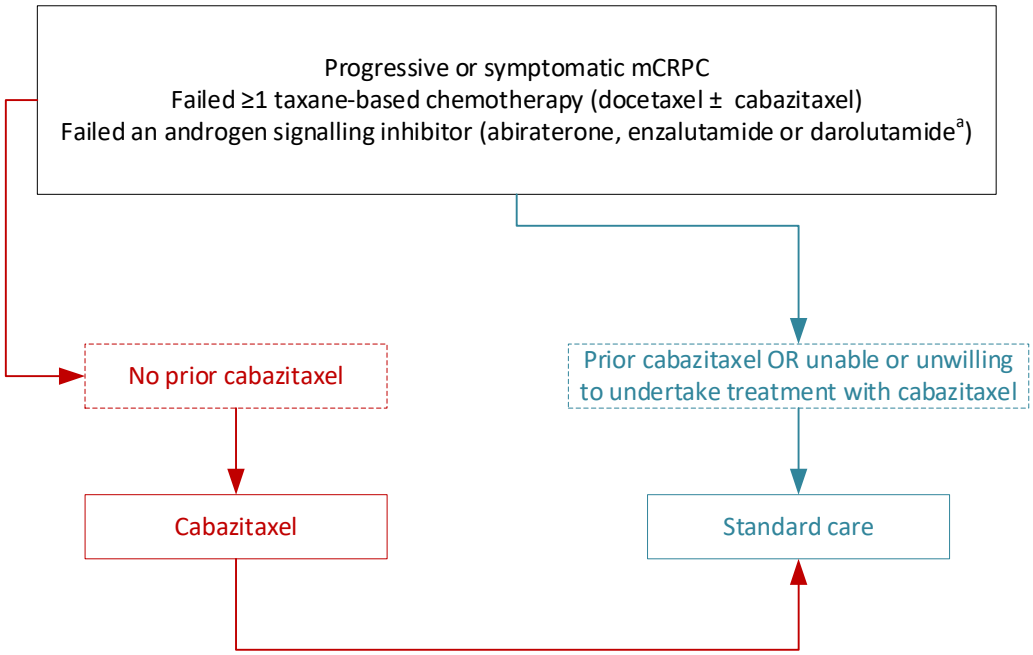

Figure 2 Current clinical management algorithm developed during the writing of the PICO

[a] the applicant anticipates darolutamide to be PBS listed metastatic disease status agnostic

The current treatment algorithm indicates that for patients with progressive or symptomatic mCRPC who have failed at least one taxane-based chemotherapy and one ASI, that the treatment options are cabazitaxel (for those who have not had prior cabazitaxel) and standard care (for those who have had prior cabazitaxel or those who are unable or unwilling to undertake treatment with cabazitaxel). The application

did not provide an estimate of the proportion of patients who would currently undergo treatment with cabazitaxel versus standard care. This will need to be clarified in the assessment report.

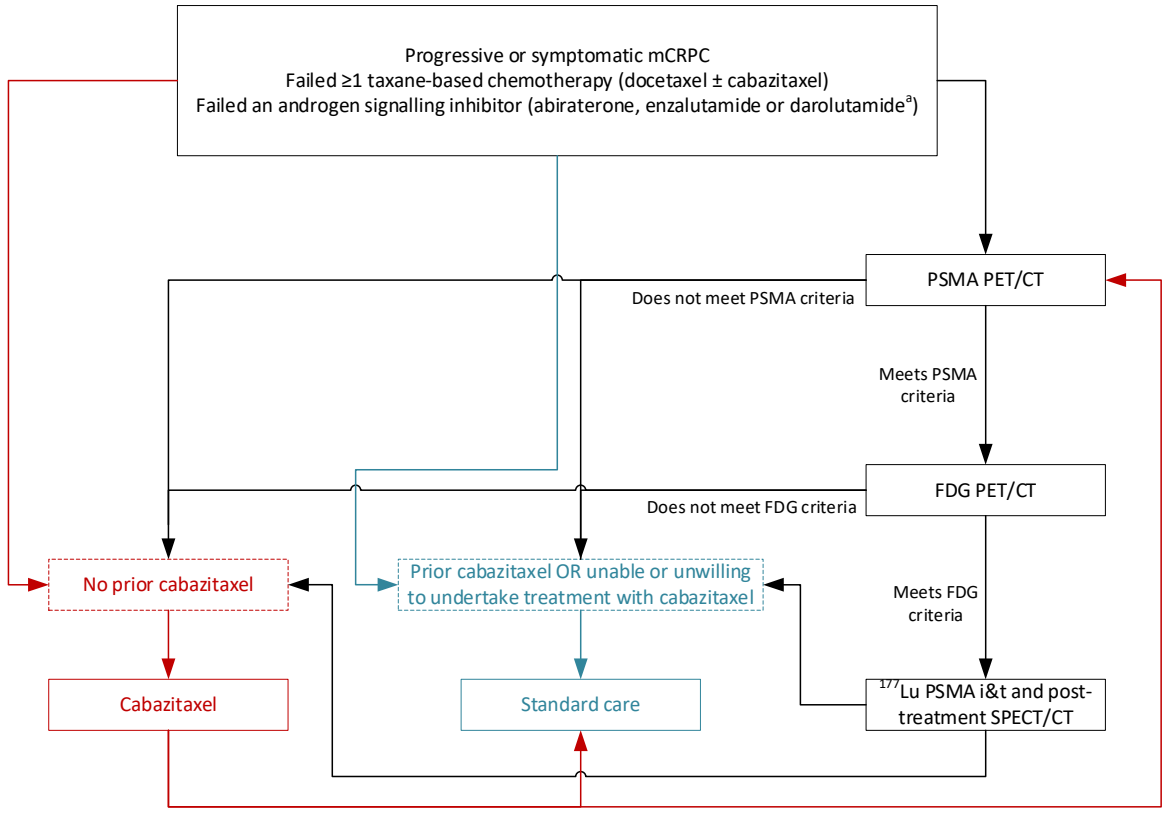

Figure 3 Proposed clinical management algorithm developed during the writing of the PICO, based on the request in the application and on the TheraP trial (Hofman 2021)

[a] the applicant anticipates darolutamide to be PBS listed metastatic disease status agnostic

The proposed algorithm, based on the request in the application and on the TheraP trial (Hofman 2021), maintains the treatment options for available in the current algorithm, however patients now have the opportunity to undergo testing with PSMA PET/CT, if they meet the criteria, then proceed to FDG PET/CT and if they meet those criteria, will be treated with ^{177}Lu PSMA I&T and undergo post-treatment SPECT/CT. Among those who meet the PSMA PET/CT criteria, but fail the FDG PET/CT criteria and those who fail to meet the PSMA PET/CT criteria, the treatment options are cabazitaxel (for those who have not had prior cabazitaxel) and standard care (for those who have had prior cabazitaxel or those who are unable or unwilling to undertake treatment with cabazitaxel). The applicant suggests that only 30% of those treated with ^{177}Lu PSMA I&T would continue to treatment with cabazitaxel. This will need to be clarified in the assessment report.

PASC accepted the clinical management algorithms and emphasised the importance of providing estimates around the proportion of patients for whom standard care would be a relevant comparator, and the proportion of those who would continue to treatment with cabazitaxel following ^{177}Lu PSMA.

Figure 4 was developed for the post-PASC PICO to capture a proposed algorithm where eligibility for ^{177}Lu PSMA I&T treatment does not require FDG PET/CT and also does not include post-treatment SPECT/CT, as per the VISION trial (Sartor 2021).

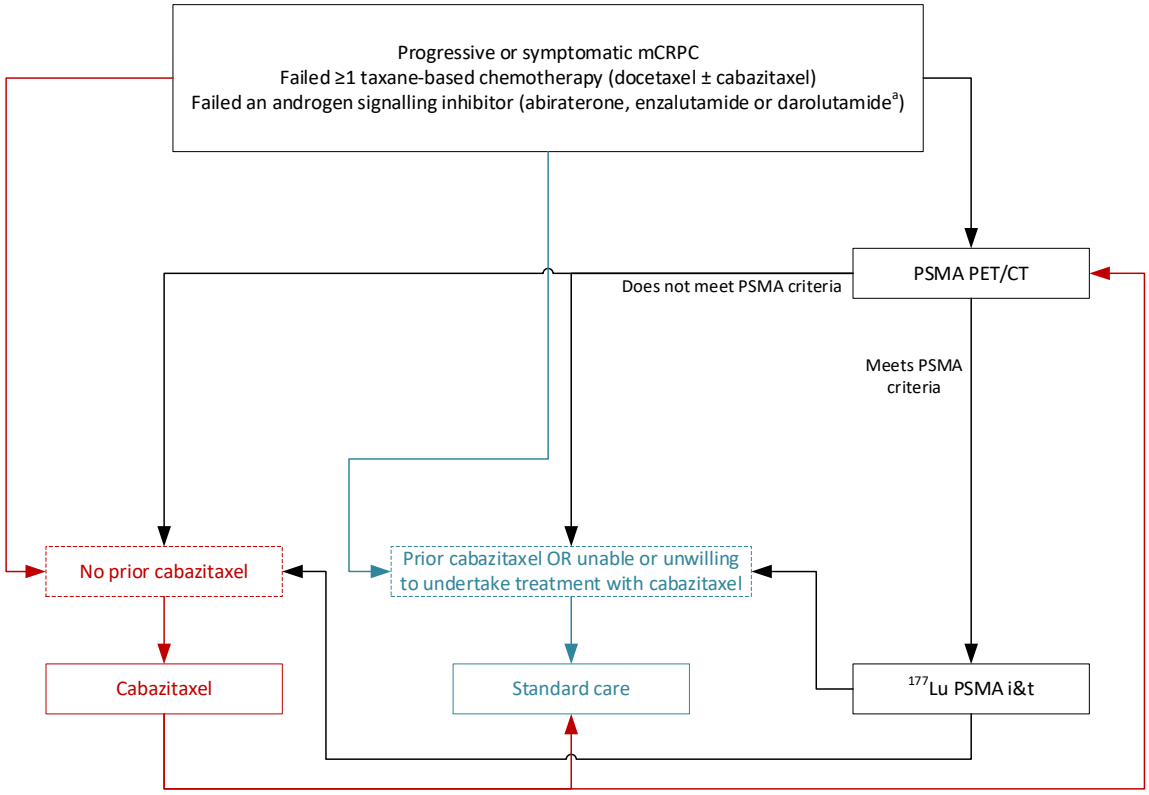

Figure 4 Possible clinical management algorithm developed during the writing of the PICO, based on the VISION trial (Sartor 2021)

[a] the applicant anticipates darolutamide to be PBS listed metastatic disease status agnostic

*PASC reiterated the need for the assessment report to provide comparisons with a possible clinical management algorithm which does not include FDG-PET (*Figure 4*).*

Proposed economic evaluation

Table 3 provides a guide for determining which type of economic evaluation is appropriate. Based on the clinical claim of superior health outcomes for effectiveness (a clinical claim regarding comparative safety is required from the applicant), a cost-effectiveness or cost-utility analysis would be appropriate. There is some randomised trial evidence that would appear to support this approach (the TheraP [versus cabazitaxel; Hofman 2021] and VISION [versus placebo; Sartor 2021] trials).

PASC noted that no comparative safety claim was made by the application. PASC also noted that the comparative safety of ^{177}Lu PSMA appeared to be superior compared with cabazitaxel (TheraP, Hofman 2021) and inferior compared with standard care (VISION; Sartor 2021).

PASC accepted that a cost-effectiveness or cost-utility analysis would be appropriate based on the clinical claim of superior effectiveness.

Table 3 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
? = reflect uncertainties and any identified health trade-offs in the economic evaluation, as a minimum in a cost-consequences analysis
[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

Proposal for public funding

The application requested a single MBS item, but that has since been updated to three to include the PSMA and FDG PET/CT scans. The proposed items, drafted by the applicant, are presented in the tables below; suggested amendments to the item descriptors are denoted by italicised text (additions) or struck through text (deletions).

Category 5 - Diagnostic Imaging Services
MBS item XXXX Whole body prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/computerised tomography (CT) study, performed for the assessment of suitability for 177 Lu -PSMA therapy in a patient with metastatic castrate resistant prostate cancer who has previously received a taxane chemotherapy and androgen signalling inhibitor. Applicable only once per lifetime
Fee $1400

The item descriptor and requested fee are consistent with those considered and supported by MSAC in its consideration of the MSAC 1632 application (MSAC 1632 PSD, July 2021). *PASC noted the requested fee for PSMA PET/CT was the same as that supported by MSAC in July 2021 for PSMA PET/CT in the context of MSAC 1632.*

PASC suggested the applicant reconsider the limitation of the PSMA PET/CT to 'once per lifetime' which would prohibit reassessment prior to subsequent ^{177}Lu PSMA treatment cycles.

Category 5 - Diagnostic Imaging Services
MBS item YYYY Whole body F18 Fluorine deoxyglucose (FDG) positron emission tomography (PET)/computerised tomography (CT) study, performed for the assessment of suitability for 177 Lu -PSMA therapy in a patient with metastatic castrate resistant prostate cancer who has previously received a taxane chemotherapy and androgen signalling inhibitor, and in whom a PSMA PET undertaken with the previous 60 days has demonstrated suitability for 177 Lu PSMA therapy (PSMA PET demonstrating an SUV max >15 at a single site of disease and SUVmax >10 at all sites of measurable disease). Applicable only once per lifetime
Fee $1000

The requested fee is similar to current fees for whole body FDG PET/CT currently listed on the MBS, which range from $953.00 to $999.00 for the PET component (see Table 4 in the attachment) plus $100 for the associated CT component (MBS item 61505). *PASC requested that the applicant justify the proposed fee for FDG PET/CT, which would need to be considered by MSAC.*

PASC questioned the requirement that FDG PET/CT be conducted within 60 days of the PSMA PET/CT. PASC suggested the applicant reconsider this lengthy interval. PASC requested that, overall, any minimum or maximum time intervals between any of the codependent elements be included where appropriate in the proposed item descriptors and a justification provided for each such interval.

Category 3 – Therapeutic Procedures T3. Therapeutic Nuclear Medicine
MBS item ZZZZ *Administration of* Lu PSMA therapy for treatment of ~~men~~ *patients* with progressive metastatic castrate resistant prostate cancer after disease progression on chemotherapy and at least one androgen signalling inhibitor *and imaging (Lu PSMA single-photon emission computed tomography (SPECT)/computerised tomography (CT)) involving a whole-body scan acquired 24 hours following injection.*
Fee: $8000 *Benefit: 85% = $6800*

The proposed fee for ^{177}Lu PSMA I&T was updated from $7000 per dose ($5500 for ^{177}Lu PSMA I&T production and administration plus $1500 for post-therapy SPECT scan) in the application to $8000 ($5500 for preparation of ^{177}Lu PSMA I&T plus $2500 for administration, immediate aftercare, and 24-hour post-therapy SPECT/CT). Although the requested fee includes the post-therapy SPECT/CT scan, the proposed item descriptor did not specify this, and so this has been included in the revised item descriptor above. The fee for ^{177}Lu PSMA I&T and the post-treatment ^{177}Lu SPECT/CT scan will need to be justified in the assessment report.

PASC noted that the proposed descriptor for ^{177}Lu PSMA therapy (Item ZZZZ) was agnostic to ^{177}Lu PSMA ligands and considered this appropriate subject to demonstration of therapeutic equivalence between ligands as previously requested.

PASC discussed the requested fee breakdown for ^{177}Lu PSMA including:

- *manufacture of ^{177}Lu PSMA;*
- *administration of ^{177}Lu PSMA; and*
- *post-treatment SPECT/CT.*

PASC considered that appropriate fee justification was required in the assessment report, including the use and cost of post-treatment SPECT/CT.

PASC stated that there should be no co-claiming of specialist/consultant physician consultation items with the proposed item combining ^{177}Lu PSMA and subsequent SPECT/CT.

PASC advised that the item descriptors include reference to MDTs and referring clinicians, which was suggested to be restricted to medical oncologists.

PASC advised that details regarding training and accreditation of providers be addressed and was aware that those developed by the Committee for Joint College Training (CJCT) still needs formal approval and endorsement by the Royal Australasian College of Physicians (RACP) and the Royal Australian and New Zealand College of Radiologists (RANZCR).

Summary of public consultation input

Input type	Number of comments received
Responses from groups/organisations	18
Responses from individuals	23
Individuals — medical professionals	*2*
Individuals — consumers	*19*
Individuals — care givers	*2*
Total all Input	**41**

The following organisations provided input on the application:

1. GenesisCare
2. Advanced Prostate Cancer Support Group Australia
3. St Vincent's Health Australia
4. Prostate Cancer Foundation Australia
5. Tamworth Prostate Cancer Support Group
6. Prostate Heidelberg Cancer Support Group (PHCSG)
7. Prostate Cancer Foundation Australia
8. Urological Society of Australia and New Zealand (USANZ)
9. South Eastern Prostate Cancer Support Group
10. Applied Molecular Therapies (AMT)
11. Peter MacCallum Cancer Centre
12. Australasian Association of Nuclear Medicine Specialists (AANMS)
13. Movember
14. Royal Australian and New Zealand College of Radiologists (RANZCR)
15. Australian and New Zealand Society of Nuclear Medicine (ANZSNM)
16. Australian Radiopharmaceutical Trials Network (ARTnet)
17. Norvatis
18. Telix Pharmaceuticals.

All organisations were supportive of the application, apart from RANZCR and two competitor companies. All consumers and specialists were supportive of the application. RANZCR was concerned that there is no

policy framework in place for theranostics before MSAC considers this application, and it does not support the AANMS Position Statement of Practice of Theranostics.

Benefits

Organisations and specialists considered that the proposed treatment is well tolerated by patients, improves progression free and overall survival and quality of life for patients with advanced prostate cancer. The USANZ noted that this treatment would provide another layer of treatment for patients who received all available treatment. It was also noted that the treatment provides improved palliation, improved mobility and could lead to reduced hospital admission and reduced need for palliative care services. Consumers noted benefits relating to extension of life, improvement in quality of life and wellbeing for themselves, their carers, family, and friends.

Consumers and consumer organisations considered that public funding would make this treatment more accessible and affordable, which would provide more equitable access to this treatment.

The USANZ considered that this treatment must be administered in collaboration with nuclear radiologists, radiation oncologist and medical oncologists as part of a multidisciplinary team. Other organisations and specialists noted that services associated with the proposed treatment would be routine pathology (blood) tests, monitoring PSA levels, and PSMA PET-CT and FDG PET/CT scans for confirmation and location of prostate metastases and to select that patients who are most likely to benefit from the treatment. GenesisCare noted that FDG PET is not routinely used in screening globally and based on the VISION trial, not required in significantly improving patient outcomes. GenesisCare considered the cut-off for platelets of >75 x 10^9/L for patients to be too low, as most trials have specified platelets to be >100 x 10^9/L.

Most responses agreed with the proposed treatment cost. However, GenesisCare considered that the costs were underestimated, as the cost of the isotope would be around $6,000, and costs associated with the physician, physicist, nurse, IV fluids, facility fee and dosimetry imaging would also need to be considered. A specialist noted that the proposed fee appeared to be based on at-cost pricing of ^{177}Lu.

Disadvantages

GenesisCare considered that the main disadvantage would be the need for specialised facilities to safely administer this treatment and enough practitioners trained in this specialised area of medicine.

Two competitor companies consider that there was insufficient evidence to support the application's claim that ^{177}Lu PSMA I&T and ^{177}Lu PSMA 617 are equivalent, and that the limited body of available data does not allow for a reliable clinical comparison of biodistribution between ^{177}Lu PSMA 617 and ^{177}Lu PSMA I&T. It was noted that there weren't any randomised controlled trials to confirm the safety, efficacy, and favourable benefit-risk profile of this agent, nor any study investigating the optimum administered activity, number of cycles, or interval between cycles.

One competitor company noted that ^{177}Lu PSMA I&T is proposed to be produced under TGA exemption in public hospitals. It considered that this would limit the availability of the service and may result in variable service due to the lack of regulated quality standards and oversight.

PASC noted there was a significant volume of consultation feedback.

Next steps

The applicant advised this application will be progressing as an ADAR (applicant-developed assessment report).

Applicant comment on ratified PICO Confirmation

Population

The applicant indicated that they would address the points raised by PASC in the ADAR.

Intervention

The applicant acknowledged the issues raised by PASC and proposed a simplified treatment algorithm that omits the requirement for confirmatory FDG PET/CT testing for ^{177}Lu PSMA i&t eligibility. However, the applicant advised that the ADAR will still consider the evidence for FDG PET/CT testing and the economic evaluation will include scenario analyses including FDG PET/CT.

In response to the consideration by the MSAC Executive, the applicant stated that ^{177}Lu PSMA-617 is radio-equivalent to ^{177}Lu PSMA i&t, meaning the radiation dose delivered to tumour and non-tumour organs are equivalent between both agents. The applicant advised that, importantly, patient outcomes between both agents have been shown to be equivalent. The applicant further stated that they will present the best available evidence to support this claim.

Comparator

The applicant indicated that they would address the points raised by PASC in the ADAR.

Reference standard

The applicant indicated that they would address the points raised by PASC in the ADAR.

Clinical utility standard

The applicant indicated that they would address the points raised by PASC in the ADAR.

Clinical Management Algorithms

The applicant indicated that they would address the points raised by PASC in the ADAR.

Proposed economic evaluation

The applicant indicated that they would address the points raised by PASC in the ADAR.

Proposal for public funding

The applicant advised that they no longer propose FDG PET/CT confirmatory testing to inform eligibility for ^{177}Lu PSMA i&t treatment.

The applicant has advised that they will provide a breakdown of each cost component to justify the proposed fee of $8,000 per dose for ^{177}Lu PSMA i&t.

Attachment

Table 4 Current MBS items for FDG PET

MBS item	Indication	Fee
61523	Whole body: evaluation of a solitary pulmonary nodule where the lesion is considered unsuitable for transthoracic fine needle aspiration biopsy, or for which an attempt at pathological characterisation has failed	$953.00
61524	Whole body: staging of locally advanced (Stage III) breast cancer, for a patient who is considered suitable for active therapy	$953.00
61525	Whole body: evaluation of suspected metastatic or suspected locally or regionally recurrent breast carcinoma, for a patient who is considered suitable for active therapy	$953.00
61529	Whole body: staging of proven non-small cell lung cancer, where curative surgery or radiotherapy is planned	$953.00
61538	Brain: Evaluation of suspected residual or recurrent malignant brain tumour based on anatomical imaging findings, after definitive therapy (or during ongoing chemotherapy) in patients who are considered suitable for further active therapy	$901.00
61541	Whole body: following initial therapy, for the evaluation of suspected residual, metastatic or recurrent colorectal carcinoma in patients considered suitable for active therapy	$953.00
61553	Whole body: following initial therapy, performed for the evaluation of suspected metastatic or recurrent malignant melanoma in patients considered suitable for active therapy	$999.00
61559	Brain: evaluation of refractory epilepsy which is being evaluated for surgery	$918.00
61560	Brain: diagnosis of Alzheimer's disease	$605.05
61565	Whole body: following initial therapy, performed for the evaluation of suspected residual, metastatic or recurrent ovarian carcinoma in patients considered suitable for active therapy	$953.00
61571	Whole body: further primary staging of patients with histologically proven carcinoma of the uterine cervix, at FIGO stage IB2 or greater by conventional staging, prior to planned radical radiation therapy or combined modality therapy with curative intent	$953.00
61575	Whole body: further staging of patients with confirmed local recurrence of carcinoma of the uterine cervix considered suitable for salvage pelvic chemoradiotherapy or pelvic exenteration with curative intent	$953.00
61577	Whole body: staging of proven oesophageal or GEJ carcinoma, in patients considered suitable for active therapy	$953.00
61598	Whole body: staging of biopsy-proven newly diagnosed or recurrent head and neck cancer	$953.00
61604	Whole body: evaluation of patients with suspected residual head and neck cancer after definitive treatment, and who are suitable for active therapy	$953.00
61610	Whole body: evaluation of metastatic squamous cell carcinoma of unknown primary site involving cervical nodes	$953.00
61620	Whole body: initial staging of newly diagnosed or previously untreated Hodgkin or non-Hodgkin lymphoma	$953.00
61622	Whole body: assess response to first line therapy either during treatment or within three months of completing definitive first line treatment for Hodgkin or non-Hodgkin lymphoma	$953.00
61628	Whole body: restaging following confirmation of recurrence of Hodgkin or non-Hodgkin lymphoma	$953.00
61632	Whole body: assess response to second-line chemotherapy if haemopoietic stem cell transplantation is being considered for Hodgkin or non-Hodgkin lymphoma	$953.00
61640	Whole body: initial staging of patients with biopsy-proven bone or soft tissue sarcoma (excluding gastrointestinal stromal tumour) considered by conventional staging to be potentially curable	$999.00
61646	Whole body: evaluation of patients with suspected residual or recurrent sarcoma (excluding gastrointestinal stromal tumour) after the initial course of definitive therapy to determine suitability for subsequent therapy with curative intent	$999.00

Source: MBS online (http://www.mbsonline.gov.au/internet/mbsonline/publishing.nsf/Content/Home)

Table 5 PBS restrictions for ASIs (abiraterone, enzalutamide) and cabazitaxel

Abiraterone Castration resistant metastatic carcinoma of the prostate Clinical criteria: • The treatment must be used in combination with a corticosteroid, AND • The treatment must not be used in combination with chemotherapy, AND • Patient must have a WHO performance status of 2 or less, AND • Patient must not receive PBS-subsidised abiraterone if progressive disease develops while on abiraterone, AND • Patient must not have received prior treatment with enzalutamide; OR • Patient must have developed intolerance to enzalutamide of a severity necessitating permanent treatment withdrawal.
Enzalutamide Castration resistant metastatic carcinoma of the prostate Clinical criteria: • The treatment must not be used in combination with chemotherapy, AND • Patient must have a WHO performance status of 2 or less, AND • Patient must not receive PBS-subsidised treatment with this drug if progressive disease develops while on this drug, AND • Patient must not have received prior treatment with abiraterone; OR • Patient must have developed intolerance to abiraterone of a severity necessitating permanent treatment withdrawal.
Cabazitaxel Castration resistant metastatic carcinoma of the prostate Clinical criteria: • The treatment must be in combination with prednisone or prednisolone, AND • The treatment must not be used in combination with abiraterone, AND • Patient must have failed treatment with docetaxel due to resistance or intolerance, AND • Patient must have a WHO performance status of 2 or less, AND • Patient must not receive PBS-subsidised cabazitaxel if progressive disease develops while on cabazitaxel.

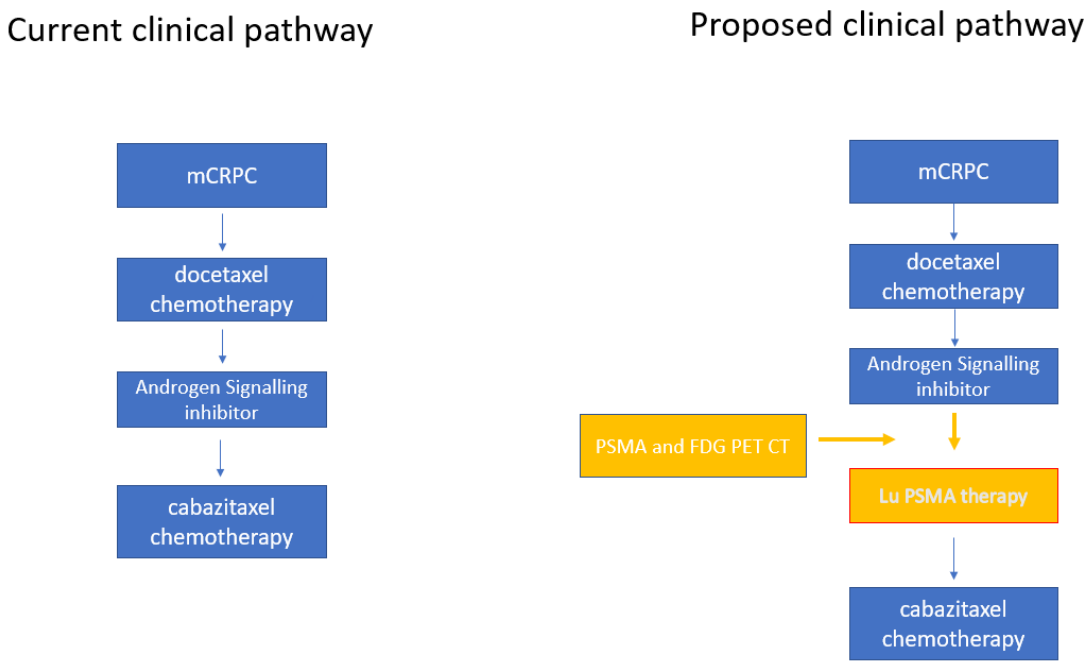

Figure 5 Current and proposed clinical management algorithms presented in the application
Source: p25 of the application

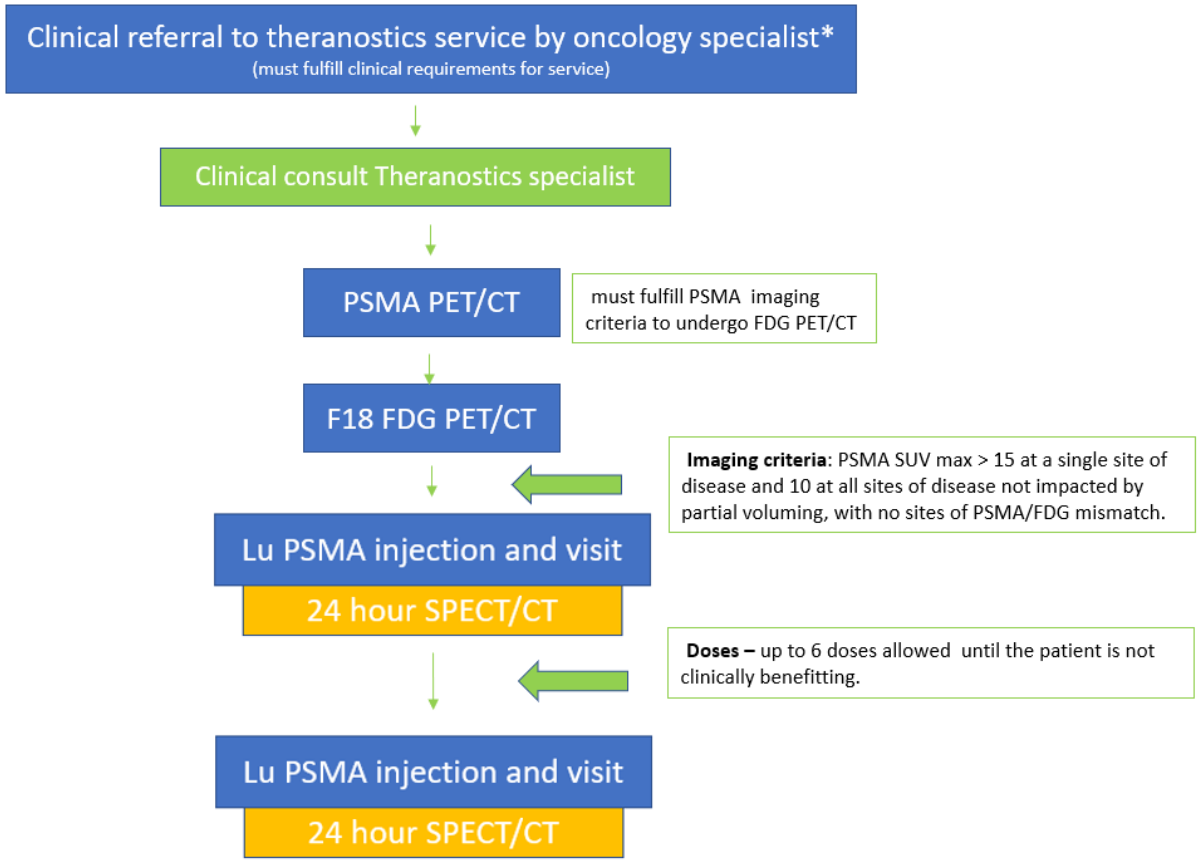

Figure 6 Updated proposed clinical management algorithm provided by the applicant
Source: provided by the applicant

References

Australian Government Department of Health. 2021. PET unit locations by Australian state and territory [Online]. https://www1.health.gov.au/internet/main/publishing.nsf/Content/pet-unit-locations#NTPET

Emmett L, et al. 2019. Results of a Prospective Phase 2 Pilot Trial of ^{177}Lu-PSMA-617 Therapy for Metastatic Castration-Resistant Prostate Cancer Including Imaging Predictors of Treatment Response and Patterns of Progression. *Clinical Genitourinary Cancer,* 17(1): 15-22.

Hofman MS, et al. 2021. [^{177}Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial. *Lancet*, 397:797-804.

Hofman MS & Hicks RJ. 2016. How We Read Oncologic FDG PET/CT. *Cancer Imaging,* 16: 35.

Hofman MS, et al. 2020. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. *Lancet*, 395: 1208-1216.

Kulkarni HR, et al. 2016. PSMA-Based Radioligand Therapy for Metastatic Castration-Resistant Prostate Cancer: The Bad Berka Experience Since 2013. *J Nucl Med*. 57(Suppl 3):97S-104S. doi: 10.2967/jnumed.115.170167. PMID: 27694180.

MSAC 1618 PSD, April 2021 MSAC meeting. http://www.msac.gov.au/internet/msac/publishing.nsf/Content/19F02703F69D97C9CA258522001DE2DA/$File/1618%20Final%20PSD%20-%20Mar-Apr%202021_redacted.pdf

MSAC 1632 Public Summary Document. 2021. Application 1632 – PSMA PET/CT imaging for informing treatment of patients with prostate cancer. http://www.msac.gov.au/internet/msac/publishing.nsf/Content/B2B42D6E89D50ED8CA258570001ED449/$File/1632%20Final%20PSD%20-%20July%202021.pdf

MSAC 1632 Ratified PICO Confirmation. 2020. PSMA PET/CT imaging for informing treatment of patients with Prostate Cancer. http://www.msac.gov.au/internet/msac/publishing.nsf/Content/B2B42D6E89D50ED8CA258570001ED449/$File/1632%20Ratified%20PICO.pdf

Olaparib PSD, March 2021 PBAC meeting. https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2021-03/files/olaparib-psd-mar-2021.pdf

Perera M, et al. 2020. Gallium-68 Prostate-specific Membrane Antigen Positron Emission Tomography in Advanced Prostate Cancer-Updated Diagnostic Utility, Sensitivity, Specificity, and Distribution of Prostate-specific Membrane Antigen-avid Lesions: A Systematic Review and Meta-analysis. *Eur Urol*, 77: 403-417.

Sadaghiani MS, et al. 2021. A Systematic Review and Meta-analysis of the Effectiveness and Toxicities of Lutetium-177-labeled Prostate-specific Membrane Antigen-targeted Radioligand Therapy in Metastatic Castration-Resistant Prostate Cancer. *Eur Urol*. 80(1):82-94. doi: 10.1016/j.eururo.2021.03.004. Epub 2021 Apr 8. PMID: 33840558; PMCID: PMC8206006.

Sartor O, et al. 2021. Lutetium-177–PSMA-617 for Metastatic Castration-Resistant Prostate Cancer. *New England Journal of Medicine*, 385(12): 1091-1103.

Scott AM. 2001. Current status of positron emission tomography in oncology. *Intern Med J*, 31, 27-36.