



Australian Government
Medical Services Advisory Committee

Public Summary Document

Application No. 1455 – Proton Beam Therapy for patients supported under the Medical Treatment Overseas Program

Applicant: Department of Health

Date of MSAC consideration: MSAC 74th Meeting, 22-23 November 2018

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#)

1. Purpose of application

The Minister of Health referred to MSAC the question of public funding arrangements for proton beam therapy (PBT), a type of particle therapy for the limited clinical indications which are supported by the Medical Treatment Overseas Program (MTO). The Minister noted that this assessment may be a precursor to broader MSAC assessment of PBT for other indications. To inform the MSAC advice, an assessment report was prepared through a contract managed by the Department of Health.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness in comparison with existing radiation treatments (typically photons) or other options, MSAC did not support funding of proton beam therapy for all indications. MSAC also noted that proton beam therapy is a highly specialised intervention which requires unique specialist infrastructure and workforce.

MSAC considered the safety and effectiveness of proton beam therapy in adult brain/spinal/paraspinal tumours, ocular tumours, paediatric/adolescent tumours and other tumours (specifically neuroblastoma and adenoid cystic carcinoma).

MSAC considered that proton beam therapy has likely similar effectiveness to photon radiation therapy overall, but evidence of superior safety over photon radiation therapy exists only in paediatric tumours, with the most persuasive case being for paediatric brain or spinal tumours, and possibly a subset of adult brain or spinal tumours.

MSAC considered that the economic evaluation did not support a conclusion that proton beam therapy would be acceptably cost-effective, but would welcome a more completely informed economic evaluation.

In the context of raising these issues for resolution, MSAC acknowledged that currently a small number of Australian patients have to travel overseas for this treatment under the

Medical Treatment Overseas Program (MTOP). MSAC noted that there was likely a dosimetric advantage for the treatment of some, but not all, types of tumour with proton beam therapy over conventional radiotherapy with photons. Given the last decade has seen significant technical improvements in the delivery of conventional radiotherapy, MSAC considered it was important to provide justification for which tumours should be treated with protons rather than conventional modalities of radiation therapy using photons.

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

MSAC noted that proton beam therapy (PBT) is a form of external beam radiation therapy that uses heavier particles (protons) instead of X-rays (photons, which are used in conventional radiotherapy).

As proposed, the service would be exclusively used in purpose-built proton beam facilities for the treatment of range of tumours including paediatric tumours, ocular tumours and craniospinal malignancies. The target population would include people with rare cancers who are currently eligible for overseas PBT funding through the MTOP. Use of the technology in the target population and setting would lead to some patients being able to access other funded services and products for the curative or salvage treatment of rare cancers in Australia. PBT can be used either as monotherapy, as a 'boost' mechanism to conventional photon radiation therapy (PRT), or in combination with other modalities such as chemotherapy and surgery.

The claimed advantage of PBT over other forms of radiotherapy is in improved radiation distribution (Bragg peak) which reduces the radiation dosage to nearby organs. The result is a higher dose of radiation to the tumour with fewer side effects. However, MSAC noted that this theoretical advantage was only acceptably supported by the results of retrospective studies involving paediatric tumours and possibly adult brain or spinal tumours, and this supported advantage was limited to a comparative safety advantage of PBT for these tumour types.

MSAC noted that, despite likely dosimetric benefits, evidence of the comparative clinical effectiveness of PBT is limited due to the small number of randomised controlled trials and the rarity of tumours usually treated by protons. The available clinical data do not clearly demonstrate a comparative effectiveness advantage of PBT for any tumour type. MSAC noted that there are currently phase II and phase III randomised controlled trials underway; however, the first phase III trial will not be completed until 2024.

MSAC noted that a cost-consequence economic evaluation was used, due to translational issues and because of uncertainties in the quality and gaps in the evidence base. The comparator was photon radiation therapy (PRT). Some indicative health outcome consequences were quantified, but incremental costs were not compared to incremental health outcomes. Some healthcare resource consequences of differences in adverse event rates were estimated, but these estimated cost off-sets were small and uncertain.

The capital cost of PBT relative to conventional PRT was not included in the modelling. The cost of a PBT facility was estimated in the 2017 HealthPact Report on Proton and Heavy Ion Therapy (equipment only) as being around AUD \$34-260 million for a single to multi-room facility, with staffing costs of \$10.4 million, and operational costs for a three room facility of \$8.8 million annually as compared to a double room conventional PRT centre with \$5 million publicly reported costs, staffing costs of \$4.25 million annually, and operational costs of \$4.51 million annually.

MSAC noted that the cost of services provided using PBT would be roughly 1.5–2.5 times more than PRT. This suggests that PBT would need to be priced higher than PRT to recover costs of delivering the service. MSAC noted that, even if the cost of delivering PBT reduces over time, there will always be a substantial staffing requirement, and operating costs will always be high.

MSAC noted issues with the financial/budgetary impacts provided and considered the estimated numbers to be highly uncertain. The assessment report provided data from 2009 and extrapolated to estimate the population in 2016, rather than using more recent data. The annual cost of the new service could be above \$37million. The cost offsets are also uncertain.

In terms of service delivery, MSAC noted that there is currently limited expertise with PBT in Australia, and therefore a significant amount of training is required before a new centre can deliver results to the same high standard as established centres. There is a requirement for multidisciplinary integrated team care. Accreditation, certification and compliance with dosimetric standards are also required. In particular, medical physicists are needed for quality assurance of the proton beam, given the close proximity of the planned tumour volume and the organs at risk (vital normal structures) for most clinical indications for PBT. MSAC noted that there is already a shortage of medical physicists in Australia.

MSAC noted that there have been 66 approved applications for PBT in 20 years of the MTOP running; the number of eligible patients is therefore small. MSAC acknowledged that, at the individual level, patients who need PBT currently have to travel overseas at great personal cost to themselves and their carers. However, MSAC also noted that MTOP has been the most cost-efficient way to provide PBT to Australians, and the program would continue until a PBT facility is operational in Australia.

4. Background

There are currently no PBT facilities in Australia. There is no mechanism for private or public funding of PBT, except for patients who have been funded to travel overseas for PBT through the MTOP. The MTOP criteria are:

- a. the proposed overseas treatment or an effective alternative treatment must not be available in Australia in time to benefit the applicant;
- b. the treatment must be significantly life extending and potentially curative;
- c. there must be a real prospect of success for the applicant; and
- d. the treatment must be accepted by the Australian medical profession as a standard form of treatment for the applicant's condition.

To qualify for the MTOP, the applicant must be an Australian citizen or be an Australian resident eligible to receive Medicare Benefits.

5. Prerequisites to implementation of any funding advice

The devices listed in Table 1 are included on the Australian Register of Therapeutic Goods (ARTG).

Table 1 Proton beam therapy devices included on the ARTG

ARTG number	Product number	Product description	Product category	Sponsor
147516 (ARTG start date 21/1/2007)	47069 Proton therapy system	Proton therapy system. An assembly of devices used to produce and deliver a transverse and longitudinal dose proton beam to treat localised tumours and other conditions susceptible to treatment by radiation.	Medical Device Class IIb	<u>Proton Therapy Australia Pty Ltd.</u>
288732 (ARTG start date 9/5/2017)	45064 Digital imager, radiation therapy	Digital imager, radiation therapy. For use with a charged particle or photon radiation therapy system for localisation of the patient position with respect to the therapy equipment and to provide correction feedback to the radiation therapy device.	Medical Device Class IIb	<u>Proton Therapy Australia Pty Ltd.</u>
211837 (ARTG start date 5/7/2013)	47069 Proton therapy system	Proton therapy system. Production and delivery of a transverse and longitudinal dose proton beam to treat localised tumours and other conditions susceptible to treatment by radiation.	Medical Device Class IIb	<u>Varian Medical Systems Australasia Pty Ltd.</u>

Source: Therapeutic Goods Administration, accessed 20 July 2017. [Link to TGA.gov.au](http://www.tga.gov.au)
Abbreviations: ARTG, Australian Register of Therapeutic Goods.

6. Proposal for public funding

The proposed clinical management algorithm included in the PICO Confirmation assumes that PBT will have public funding after facilities become operational in Australia, and will provide patients with an alternative to the existing treatments available in Australia.

7. Summary of public consultation feedback/consumer issues

Fourteen responses were received by the Department during the consumer consultation process. The following summarises the consumer issues and policy impacts identified:

- Proposed population: There is a risk that patients currently eligible for financial assistance under MTOP will no longer meet MTOP eligibility criteria. Patients may need to pay the entire cost of the PBT treatment by themselves, which may cause issues of affordability and inequitable access to treatment. If a PBT facility is established in Australia, patient out of pocket expenses may also arise due to inter-state travel costs. Further, domestic demand for PBT will be highly dependent on the clinical indications that receive funding. If MBS funding is not limited to appropriate circumstances, there is a risk for PBT technology to be used to treat conditions for which there is no evidence of comparative advantage;
- Proposed intervention and outcomes: The physical characteristics of protons offer potential benefits over PRT, however, the potential benefits have not been clinically proven for most malignancies. The availability of PBT technologies in Australia will create opportunities for medical research and clinical trials. The potential benefits of PBT are a consequence of a reduced radiation dose to normal tissues around the target resulting in fewer side effects compared with other forms of radiation therapy and a reduction in the risk of radiation-related secondary tumours;
- Proposed comparator: PBT treatment planning and delivery have advanced over time, but so too have other approaches to PRT supported by MSAC, including intensity modulated radiation therapy (IMRT). Evidence of the comparative effectiveness of PBT is difficult to access due to the limited number of RCTs;

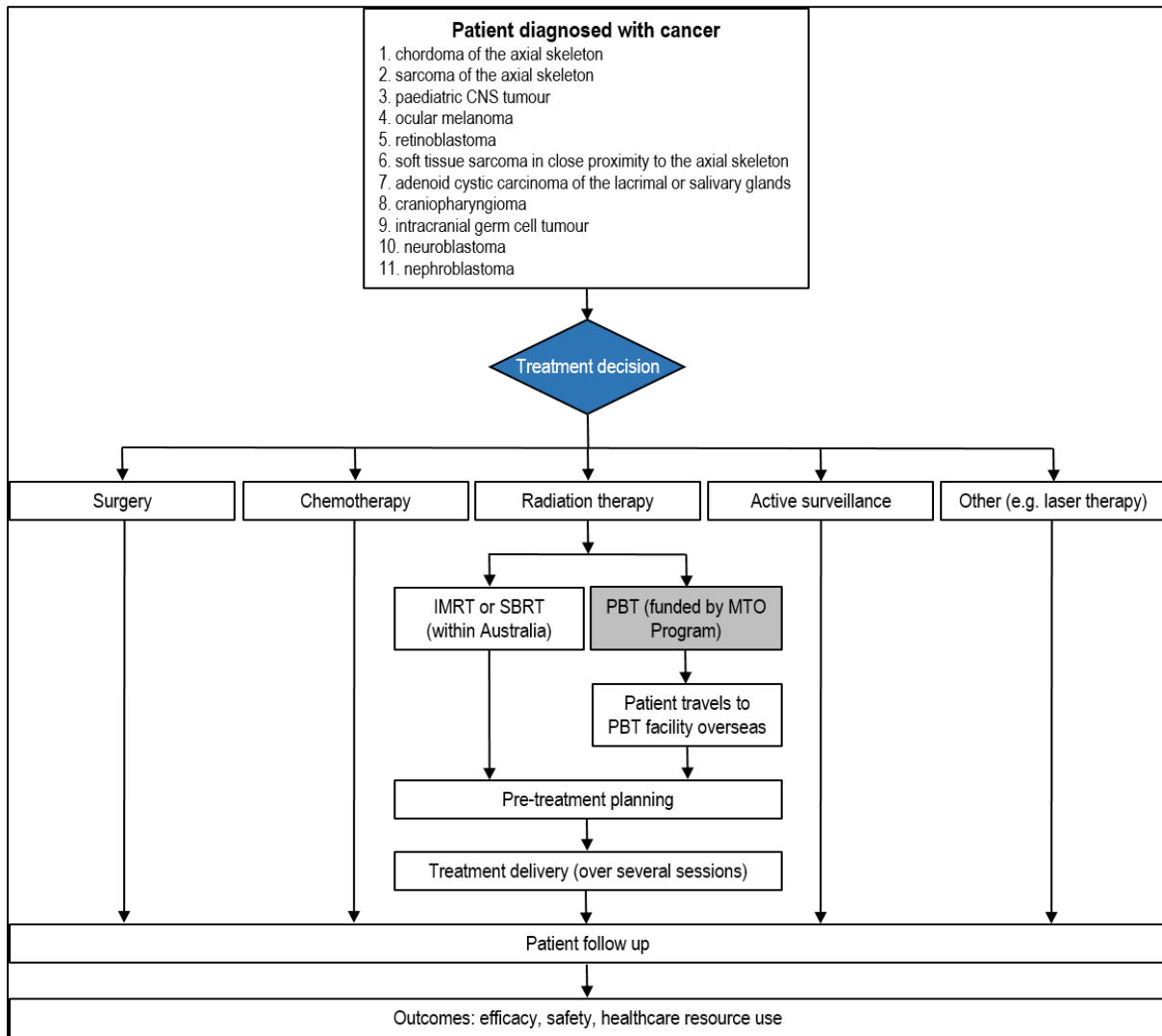
- Proposed economic analysis: PBT will require additional operational planning of increased paediatrics, anaesthetics and post treatment services i.e. occupational therapists and speech pathologists. Demand for PBT is difficult to estimate and project; and
- Clinical management: There is currently limited clinical expertise with PBT in Australia. There will be a requirement for formal particle therapy training and credentialing for radiation oncologists, medical physicists and radiation therapists from engagement of international experts.

8. Proposed intervention's place in clinical management

PBT is of particular interest in treating tumours deriving from craniospinal and ocular locations where conventional photon radiation therapy (PRT) would impose a high risk of damage to surrounding critical organs to an unacceptable level. PBT may also be the only viable curative modality available to selected paediatric and young adult cancers, where there is a critical requirement to reduce overall radiation toxicity and potential induction of secondary tumours. Case management is complex because of rarity of the cancer types, tumour location and the specialist requirements for paediatrics. The clinical case management is likely to vary based on the cancer type, disease staging, tumour location, patient prognosis and whether the treatment intent is curative or salvage treatment.

Based on the current clinical management algorithm (Figure 1), patients who receive PBT may receive financial assistance to travel overseas via MTOP. In practice, treatment of the cancers of interest may be multi-modal (e.g. radiation therapy may be used in combination with surgery).

Figure 1 Current clinical management algorithm for PBT with curative intent (generalised representation)

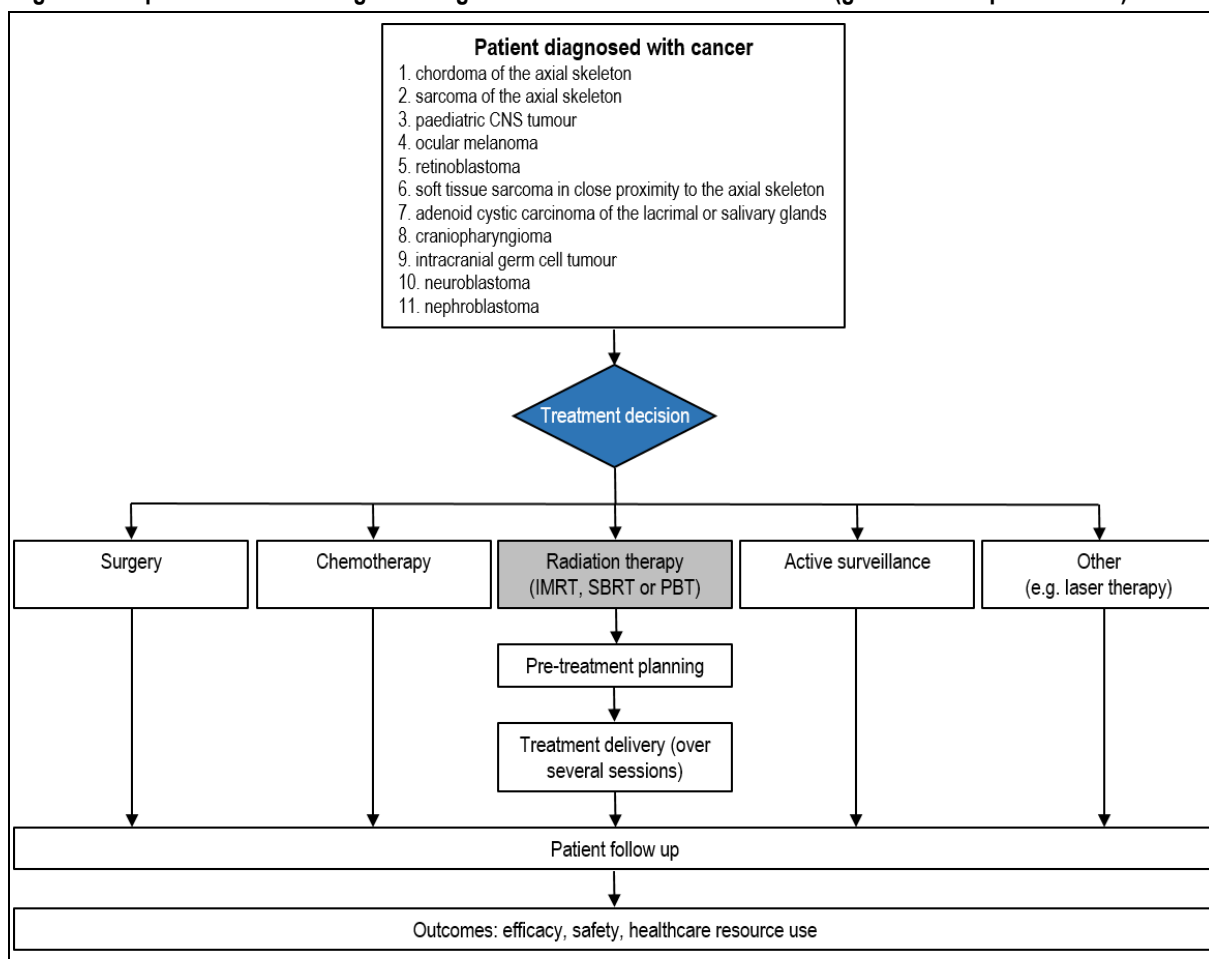


Source: Application 1455: Proton Beam Therapy (PBT) PICO Confirmation, listing the PICO-relevant cancers.

Abbreviations: PBT, proton beam therapy; CNS, central nervous system; IMRT, intensity modulated radiation therapy; SBRT, stereotactic body radiation therapy; MTO, Medical Treatment Overseas.

The proposed clinical management algorithm (Figure 2) assumes that PBT will have public funding after facilities become operational in Australia, and will provide patients with an alternative to the existing treatments available in Australia. PBT is a new technology and therefore will require the development of standard protocols, training programs and credentialing processes.

Figure 2 Proposed clinical management algorithm for PBT with curative intent (generalised representation)



Source: Application 1455: Proton Beam Therapy (PBT) PICO Confirmation, listing the PICO-relevant cancers.
Abbreviations: PBT, proton beam therapy; IMRT, intensity modulated radiation therapy; SBRT, stereotactic body radiation therapy.

9. Comparator

Potential comparators include conventional PRT including intensity modulated radiation therapy (IMRT), and stereotactic radiosurgery (SRS). Alternate external beam therapies, such as carbon ion therapy (CIT), are also relevant comparators based on the location to key organs. Other treatment options specific to the clinical condition (e.g. surgery, chemotherapy, other devices such as laser therapy for ocular tumours) are relevant comparators.

10. Comparative safety

Five systematic reviews, two previous health technology assessment reports, and 17 comparative cohort studies were collected and comprised the evidence base for the clinical evaluation of PBT.

The evidence base for the clinical evaluation of the assessment report largely comprised retrospective primary studies, with a focus on comparative effectiveness studies. There is a high risk of bias associated with the design of retrospective studies, particularly in having no control over the allocation concealment of patients into treatment arms and/or blinding of patients and researchers of allocations. There were also confounding factors in some studies, for instance, the use of unmatched mixture of tumour sizes between study arms exposed to similar radiotherapy doses, or with the variable number and/or mode of primary treatment prior to study participation.

Based on clinical findings from recently published comparative studies, PBT did not offer major safety advantages over other cancer therapies for soft tissue cancers, and ocular cancers or other PICO-relevant cancers. Conversely, PBT was found to be superior in terms of safety over PRT alternatives for paediatric cases of cancer, specifically in sparing in-field organs at risk, and in lower incidence rates of haematological radiation-induced side effects and secondary malignancies, and possibly superior in terms of safety over PRT alternatives for a subset of adult brain or spinal tumours.

Table 2 Results of key safety outcomes from systematic reviews and comparative cohort studies

Study	Outcome	Intervention n with event/N (%)	Comparator n with event/N (%)	Absolute difference (risk difference, number needed to harm)	Relative difference (relative risk, results of statistical test)
PICO 1: Brain, spinal and soft tissue cancers					
ICER (2014), Brown et al. (2013) medulloblastoma ^{a,d}	median weight loss (median % of baseline)	PBT -1.2%	PRT -5.8%	4.6%, 21.7	NR, p=0.004
	medical management of esophagitis	PBT 5%	PRT 57%	52%, 1.9	NR, p<0.001
PICO 2: Ocular cancers					
Sikuade M. et al. (2015)	retinopathy	PBT 31/106 (29%)	SRS 20/85 (24%)	5.7%, 17.5	1.2, NR
	optic neuropathy	PBT 14/106 (13%)	SRS 23/85 (27%)	13.9%, 7.2	0.5, NR
	glaucoma	PBT 5/106 (5%)	SRS 9/85 (11%)	5.9%, 17.0	0.4, NR
PICO 3: Paediatric and adolescent cancers					
Sethi R. et al. (2014)	local or in-field secondary malignancies	PBT 0/55 (0%)	PRT 4/31 (12.9%)	12.9%, 7.75	0, p=0.015
CADTH (2017), Leroy R. et al. (2016), Bishop A.J. et al. (2014)	vascular injury	PBT 2/21 (10%)	IMRT 3/31 (10%)	0%, NA	1, NS
	visual dysfunction	PBT 1/21 (5%)	IMRT 4/31 (13%)	8%, 12.5	0.38, NS
	hypothalamic obesity	PBT 4/21 (19%)	IMRT 9/31 (29%)	10%, 10	0.66, NS
	panhypopituitarism	PBT 7/21 (33%)	IMRT 17/31 (55%)	22%, 4.5	0.6, NS
	endocrinopathies (growth or sexual hormone deficiency, hypothyroidism, adrenal insufficiency)	PBT 9/21 (43%)	IMRT 7/31 (23%)	20%, 5	1.9, NS
Song S. et al. (2014)	grade 3 or 4 acute leukopenia	PBT +/- chemotherapy 16/30 (53.3%)	PRT +/- chemotherapy 10/13 (76.9%)	23.6%, 4.2	0.7, NS
	grade 3 or 4 acute thrombocytopenia	PBT +/- chemotherapy 7/30 (23.3%)	PRT +/- chemotherapy 7/13 (53.8%)	30.5%, 3.3	0.43, p=0.012
	grade 3 or 4 acute dysphagia	PBT +/- chemotherapy 14/30 (46.7%)	PRT +/- chemotherapy 2/13 (15.4%)	31.3%, 3.2	3, NS

Study	Outcome	Intervention n with event/N (%)	Comparator n with event/N (%)	Absolute difference (risk difference, number needed to harm)	Relative difference (relative risk, results of statistical test)
	acute neurological disorders	PBT +/- chemotherapy 4/30 (13.3%)	PRT +/- chemotherapy 3/13 (23%)	9.7%, 10.3	0.58, NS
	acute ophthalmic disorders	PBT +/- chemotherapy 2/30 (6.7%)	PRT +/- chemotherapy 1/13 (7.7%)	1%, 97.5	0.87, NS
Gunther J.R. et al. (2015)	grade 3 or 4 intracranial abnormalities (haemorrhaging, encephalomalacia or focal necrosis)	surgery before chemotherapy + PBT 6/16 (37.5%)	surgery before chemotherapy + IMRT 0/6 (0%)	37.5%, 2.7	NA, NR
Eaton et al. (2016)	hypothyroidism	surgery + chemotherapy + PBT 9/40 (22.5%)	surgery + chemotherapy + PRT 24/37 (64.9%)	42.4%, 2.3	0.35, p<0.001
	growth hormone deficiency	surgery + chemotherapy + PBT 21/40 (52.5%)	surgery + chemotherapy + PRT 21/37 (56.8%)	4.3%, 23.5	0.93, NS
	adrenal insufficiency	surgery + chemotherapy + PBT 2/40 (5%)	surgery + chemotherapy + PRT 3/37 (8.1%)	3.1%, 32.2	0.62, NS
	sex hormone deficiency	surgery + chemotherapy + PBT 1/40 (2.5%)	surgery + chemotherapy + PRT 7/37 (19%)	16.4%, 6.1	0.13, p=0.025
	precocious puberty	surgery + chemotherapy + PBT 7/40 (17.5%)	surgery + chemotherapy + PRT 6/37 (16.2%)	1.3%, 77.9	1.1, NS
Sato et al (2017)	intracranial vasculopathy	surgery + PBT 3/41 (7.3%)	surgery + IMRT 5/38 (13.2%)	5.8%, 17.2	0.56, NR
PICO 4: Other PICO-relevant cancers					
Romesser P.B. et al. (2016)	grade ≥2 acute dermatitis	PBT 18/18 (100%)	IMRT 17/23 (73.9%)	26.1%, 3.8	1.4, p=0.019
	grade ≥2 acute mucositis	PBT 3/18 (16.7%)	IMRT 12/23 (52.2%)	35.5%, 2.8	0.32, p=0.019
	grade ≥2 acute nausea	PBT 2/18 (11.1%)	IMRT 13/23 (56.5%)	45.4%, 2.2	0.2, p=0.003
	grade ≥2 acute dysgeusia	PBT 1/18 (5.6%)	IMRT 15/23 (65.2%)	59.6%, 1.7	0.09, p<0.001
	grade ≥2 acute dysphagia	PBT 1/18 (5.6%)	IMRT 2/23 (8.7%)	3.1%, 32.2	0.64, NS

Abbreviations: CIT, carbon ion therapy; IMRT, intensity modulated radiotherapy; NR, not reported; NS, not significant; PICO, patients intervention comparator outcomes; PBT, proton beam therapy; PRT, photon radiotherapy.

^a Extracted from Institute for Clinical and Economic Review (ICER), PBT: Final Evidence Report Washington State Health Care Authority- Health Technology Assessment. 2014 (provided in evidence pack of contracted assessment); and original source, Brown et al. (2013)

11. Comparative effectiveness

Overall, PBT was not found to substantially improve upon the benefits of alternative cancer therapies against any of the PICO-relevant cancers, however, high quality evidence was lacking in the determination of PBT effectiveness over its main comparator of interest, PRT (Table 3).

Table 3 Therapeutic profile of PBT, relative to comparators

Outcomes for PICO populations	Number of studies	Quality of evidence (GRADE) ^a	Relative to primary comparators
Safety measures for PICO 1: brain, spinal, paraspinal soft tissue cancers	1 ^a	⊕⊕⊕⊕	Uncertain
Effectiveness for PICO 1: brain, spinal, paraspinal soft tissue cancers	0	NA – no evidence identified	Uncertain
Safety measures for PICO 2: ocular cancers	1	⊕⊕⊕⊕	Uncertain
Effectiveness for PICO 2: ocular cancers	1	⊕⊕⊕⊕	Uncertain
Safety measures for PICO 3: paediatric and adolescent cancers	6	⊕⊕⊕⊕	Uncertain
Effectiveness for PICO 3: paediatric and adolescent cancers	7	⊕⊕⊕⊕	Uncertain
Safety measures for PICO 4: other populations	1	⊕⊕⊕⊕	Uncertain
Effectiveness for PICO 4: other populations	1	⊕⊕⊕⊕	Uncertain

^a GRADE Working Group grades of evidence (Atkins D. et al., 2013)¹

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

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

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

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

^a Extracted from Institute for Clinical and Economic Review (ICER), PBT: Final Evidence Report Washington State Health Care Authority-Health Technology Assessment. 2014 (provided in evidence pack of contracted assessment); and original source, Brown et al. (2013)

Clinical claim

The clinical claims were that PBT is superior in clinical effectiveness and either non-inferior or superior in safety to usual standard of care. However, the assessment report stated that there was insufficient evidence of high quality to support these claims.

12. Economic evaluation

A cost-consequences evaluation was used, due to the identified translational issues and because of uncertainties in the quality and gaps in the evidence base (Table 4).

Table 4 Summary of the economic evaluation

Perspective	Payer
Comparator	Photon radiation therapy
Type of economic evaluation	Cost-consequences
Sources of evidence	Systematic reviews, an estimate of the demand for PBT in Australia
Time horizon	Patient treatment period and time to consequences
Outcomes	Safety (recurrence, adverse events) and efficacy (survival, tumour free rate)
Methods used to generate results	Estimated medical costs and cost of adverse events from population of Australians to be treated with PBT; published methods for estimating events

Abbreviations: PBT, proton beam therapy.

Table 5 summarises the economic evaluation. In the absence of empirical estimates of comparative effectiveness, only the direction and magnitude of cost consequences can be compared.

Table 5 Summary of the economic evaluation comparison between PBT and PRT for the assessed populations

Comparison/ category	Comparative health outcomes	Medical direct cost	Transportation cost	Cost of anaesthesia	Cost of adverse events
Paediatric	Moderate evidence of < harms	PBT > PRT	PBT > PRT +	Equal	PBT < PRT
Ocular	Insufficient evidence	PBT > PRT	PBT > PRT +		Inconclusive
Brain and spinal	Moderate evidence of < harms	PBT > PRT	PBT > PRT +		PBT < PRT

Abbreviations: PBT, proton beam therapy; PRT, photon radiation therapy.

Conclusions from the economic evaluation

- There is considerable uncertainty about the comparative effectiveness between PBT and PRT. This uncertainty leads to the inability to adequately assess the cost-effectiveness of PBT. The evidence does point to some additional benefits afforded to patients who are treated for paediatric tumours. The published cost-effectiveness analyses reviewed in the assessment report lack credibility, due to the assumptions used to attempt to compensate for limited data on comparative effectiveness;
- The cost of providing PBT services is, roughly, 1.5 to 2.5 fold higher than conventional therapy in cost comparisons reported in the literature. There was no reference to the cost being equivalent to PRT;
- Applying the estimates of patients eligible for PBT made it possible to examine a rather small PICO defined population of 1,968 Australian patients directly. This approach generated an estimation of the cost and the number of adverse events from treating the eligible population. The analysis relies heavily on the accuracy of the population estimates. There are compelling arguments for the use of PBT in respect to the potential for reductions in harms due to radiation. However, the number of patients that would potentially benefit from PBT is quite small;
- The adoption of PBT has the potential of increasing MBS expenditure for radiation therapy for these patients over \$ 35 million in year one should it be priced at three times that of PRT, a reasonable percentage in an international perspective; and
- The estimate of demand for particle radiation showed that there are an estimated 58 children per year that could potentially benefit from PBT.

13. Financial/budgetary impacts

The financial implications, if public funding was via the MBS, resulting from the proposed listing of PBT are summarised in Table 6, which lists the number and costs of PBT services that would be eligible over the next five years.

Table 6 Numbers and costs of PBT services for PICO patients who are eligible

Service	2017-18	2018-19	2019-20	2020-21	2021-22
Planning number	1,968	1,993	2,018	2,043	2,068
Cost sub-total	\$16,304,614	\$16,508,422	\$16,714,777	\$16,923,712	\$17,135,258
Treatment number	64,946	65,758	66,580	67,412	68,255
Cost sub-total	\$29,631,558	\$30,001,953	\$30,376,977	\$30,756,689	\$31,141,148
Verification number	64,946	65,758	66,580	67,412	68,255
Cost sub-total	\$12,750,008	\$12,750,008	\$12,750,008	\$12,909,383	\$13,070,750
Total cost	\$58,373,309	\$59,102,975	\$59,841,762	\$60,589,784	\$61,347,157

Abbreviations: PBT, proton beam therapy; PICO, patients intervention comparator outcomes.

The overall financial implications, if public funding was via the MBS, resulting from the proposed public funding of PBT are summarised in Table 7. This table shows the costs of PBT offset by the patients who are currently treated with PRT.

Table 7 Estimated total costs to the MBS associated with PBT services offset by the reduced number PRT services

Service	2017-2018	2018-2019	2019-2020	2020-2021	2021-2022
	Cost of activities	Cost of activities	Cost of activities	Cost of activities	Cost of activities
Planning	\$9,974,972	\$10,099,659	\$10,225,905	\$10,353,729	\$10,483,150
Treatment	\$18,128,240	\$18,354,843	\$18,584,278	\$18,816,582	\$19,051,789
Verification	\$7,608,894	\$7,704,005	\$7,800,305	\$7,897,809	\$7,996,532
Sub-total costs	\$35,712,106	\$36,158,507	\$36,610,489	\$37,068,120	\$37,531,471

Abbreviations: PBT, proton beam therapy; PRT, photon radiation therapy

14. Key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
Evidence base	There is no high-level evidence for clinical benefit despite likely dosimetric benefits. Accept that high-level evidence is unlikely in paediatric cases, but request data from prospective registries (lag time ~10 years) and more data from RCTs.
Item descriptor	An item descriptor has not been specified. Item descriptors will need to be very population specific, apply only to protons (not other heavy particles). Note that an application for a re-irradiation population is likely to happen in future. Item descriptor categories could match photon treatment.
Cost	Explore cost implications for state/territory health budgets (travel/accommodation). Significant cost is expected which is unquantifiable. Therefore, request more accurate costing from relevant organisations (e.g. Bragg Centre). Explore PBT effect on Radiation Oncology Health Program Grants.
Numbers/demand	It will be difficult to estimate or predict patient throughput. Existing linear accelerators may become underutilised (only if indications outside MTOP are expanded).
Workforce	Ensure relevant colleges/organisations have processes for training, quality assurance and standards. Encourage/support collaboration/national reference group for coordination.

ESC discussion

ESC discussed that PBT is of particular interest in treating tumours deriving from craniospinal and ocular locations where conventional photon radiation therapy (PRT) would impose a high risk of damage to surrounding critical organs to an unacceptable level. The advantage of PBT over other forms of radiotherapy is in improved radiation distribution (Bragg peak) which keeps the dosage away from nearby organs. The result is a higher dose of radiation to the tumour with fewer side effects. The technology has been around for 60 years and is used overseas to treat many cancers.

There have been only 66 approved applications in 20 years of the program running. In the past 5 years, the total cost has been approximately \$2.8 million (approximately \$140,000 per patient). However, ESC noted that there may be some Australians who do not know about the program or do not want to travel, particularly those with young children.

ESC also noted that the MTOP is unlike Medicare – it is tailored to a small number of patients, and a decision is made on a case-by-case basis as to whether the patient can be treated in Australia or overseas. Applications for financial assistance under the MTOP for overseas PBT are submitted to the Department of Health. The Department of Health seeks

advice from the Faculty of Oncology within the Royal Australian and New Zealand College of Radiologists on whether the application for PBT meets the following criteria:

- a. the proposed overseas treatment or an effective alternative treatment must not be available in Australia in time to benefit the applicant;
- b. the treatment must be significantly life extending and potentially curative;
- c. there must be a real prospect of success for the applicant; and
- d. the treatment must be accepted by the Australian medical profession as a standard form of treatment for the applicant's condition.

Applications for financial assistance for PBT are not recommended in every case.

Currently, four Australian jurisdictions are considering building a PBT facility. One centre is under construction in South Australia (the Bragg Centre) which is expected to start treating patients in 2022. They expect 800 patients in the first year, with 25% from overseas.

ESC noted that no item descriptor was available or provided, but, if approved, it would be located in Category 3, Group T2 – Radiation Oncology. ESC noted that similar items would be required as those for PRT (planning, simulation, treatment, verification) but that there would be an increased cost because of increased staff time required, expensive software licences, specialist/intensive maintenance, significant electrical energy demands and senior specialised staff. The Bragg Centre has proposed costings of about double those for PRT.

ESC noted that there are 11 populations of rare cancers (based on those for PRT) with four PICO groups: adult brain/spinal (PICO 1), ocular (PICO 2), paediatric/adolescent (PICO 3) and other (nephroblastoma and adenoid cystic carcinoma) (PICO 4).

ESC noted that there are a few comparators, but only PRT is available in Australia.

ESC noted that PBT may also be the only viable curative modality available for selected paediatric and young adult cancers, where there is a critical requirement to reduce overall radiation toxicity and potential induction of secondary tumours. Case management is complex because of rarity of the cancer types, tumour location and the specialist requirements for paediatrics. The clinical case management is likely to vary based on the cancer type, disease staging, tumour location, patient prognosis, and whether the treatment intent is curative or salvage treatment.

ESC noted that the quality of clinical evidence was low; only level 3 evidence is available. There were no RCTs, but this is unsurprising, given the rare nature of the conditions being investigated.

ESC identified a number of problems with the clinical evidence:

- high risk of bias because the evidence base was largely comprised of retrospective primary studies, with a focus on comparative effectiveness studies
- marked heterogeneity because of the different conditions studied
- small numbers because of the rarity of the conditions
- outcomes/endpoints differ between studies
- no good publications comparing PBT versus PRT; given that PBT delivers radiation to the target site, it was asserted that it would be unethical to allocate patients to the alternative treatment arm, knowing that radiation can cause damage
- not all tumour types were covered and there are no data for nephroblastoma

- safety data are not available and there is a lack of quality of life data
- the comparators were variable (e.g. mixed with other modalities such as surgery and thermotherapy) and PBT was combined with PRT
- the evidence base used old proton technology (passively scattered) whereas there is now better technology in the form of pencil beam scanning.

ESC noted that the health technology assessment report prepared for the Washington State Health Care Authority (2014) rated the net health benefit of PBT relative to alternative treatments to be ‘superior’ (moderate–large net health benefit) in ocular tumours and ‘incremental’ (small net health benefit) in adult brain/spinal and paediatric cancers.

The health technology assessment report published by the Canadian Agency for Drugs and Technologies in Health (CADTH; 2017) stated that, with the low-strength quality of included primary studies in the review, clear conclusions could not be drawn regarding the benefits or harms of PBT. The agency concluded that the added cost of PBT for limited clinical benefit meant that installing PBT facilities in Canada was not well justified.

In summary, ESC noted that despite the documented dosimetric superiority of PBT over conventional radiotherapy, only low quality of evidence is available for comparative effectiveness. In addition, the evidence of comparative effectiveness is at the level of certain individual tumour types and not for the PBT service as a whole.

A number of significant issues were noted by ESC, which should be addressed:

- ESC acknowledged that having a PBT facility will be a good opportunity for research and to collect clinical data from trials, given the lack of existing data. It was noted that currently PBT is being used overseas, even with a lack of evidence, because of its perceived advantages. Therefore, there is the potential for treatment of patients with other cancers where there is no evidence of ‘advantage’.
- Consultation feedback raised the issue that an extra PICO population should be included for re-treatment/re-irradiation. The numbers in this population are unknown but could be quite large.
- ESC noted that PBT can be dangerous and requires a high level of training that is currently not available in Australia because there has been no PBT facility here until now. National standards and training programs will need to be established. There is a desire from stakeholders for a national collaborative approach, national registry and infrastructure to support this.
- Stakeholders also want a national approach to minimise the risk of uncoordinated oversupply resulting from too many Australian centres.
- Radiation Oncology Health Program Grants do not apply to a PBT facility.

For the economic evaluation, the PICO nominated cost-effectiveness or cost-utility on the basis of superior effectiveness and safety; however, the submission presented a cost-consequence analysis on the basis that superior effectiveness could not be ascertained.

ESC noted a number of problems with the economic evaluation:

- No decision tree was included, which would have informed the data to present for costs and consequences.
- There were significant translation issues (limited data from small trials) with the results not generalisable to Australia.

- The cost of simulation was not included in the economic analysis.
- The cost of intervention was based on a comparison of the cost of PBT versus intensity modulated radiation therapy (IMRT); the ratios (from six studies) ranged from 1.43 to 3.44, indicating the multiple of the cost for PBT. The submission used a ratio of 2.5 times the cost of PBT. However, ESC noted that this is not appropriate because there are four different items and some studies related to diseases like prostate cancer, which would not be treated under the proposed indications. Another large study (Peeters et al.) found a ratio of 3.2, so costs in the submission may be underestimated.
- Potential cost offsets may be an underestimate, as not all were included in the economic evaluation.
- Incremental costs were not included in the submission.
- The cost of anaesthesia cannot be equal in the cost-consequence analysis if the population is expanding.
- Hypofractionation was not considered in the economic evaluation. Because of the Bragg peak, fewer treatment sessions are needed. ESC noted that there is not a lot of data; however, if it is viable to reduce the number of treatments that would lead to cost savings.

ESC noted that paediatric cases (particularly brain tumours) require longer treatment times and more staff members, and incur higher supply and device costs. They are also likely to require anaesthesia requiring additional nursing and anaesthesia support (57% if similar to the USA; 100% was used in this submission). This may require different reimbursement to reflect the additional resources required.

ESC noted that ANSTO has done its own modelling and estimated the cost to be approximately \$50,000 per person per treatment, including capital costs and hypofractionation.

ESC noted that the assessment report calculated the operating cost associated with PBT as roughly 1.5 to 2.5 times higher than conventional therapy in cost comparisons reported from other countries. Therefore, the adoption of PBT has the potential of expanding the expenditure for radiation should it cost 2 times more than PBT. However, ESC noted issues with the financial/budgetary impacts provided and thought that the numbers are highly uncertain. The assessment report provided data from 2009 and extrapolated to estimate the population in 2016. This should have been updated with more recent data (e.g. from the Australian Institute of Health and Welfare).

From the consumer perspective, ESC noted that consumers should be aware of the risks of PBT associated with some cancers. ESC noted that there is strong support from Rare Cancers Australia to build a PBT facility in Australia. This will reduce the impact of isolation that arises from overseas travel, particularly for paediatric patients, and also reduce the costs associated with overseas travel.

15. Other significant factors

Nil

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

Nil

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website:
[visit the MSAC website](#)