Assessment of Proton Beam Therapy (PBT)

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Assessment report

VERSION CONTROL

The technical information in this document is used by the Medical Services Advisory Committee (MSAC) to inform its deliberations. MSAC is an independent committee which has been established to provide advice to the Minister for Health on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

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

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EXECUTIVE SUMMARY

Main issues for MSAC consideration

- There is a disconnect between the demonstrated clinical benefits and the documented dosimetric superiority of proton beam therapy (PBT) over conventional radiotherapy. This is tied to uncertainties and the low quality of evidence available from comparative effectiveness studies of PBT and alternative cancer treatment modalities. There is uneven clinical data coverage on certain tumour types. Evidence of comparative effectiveness and cost is at the level of individual tumour types and not for the PBT service as a whole.

- There are no results of randomised control trials (RCTs) comparing PBT to conventional radiation therapy including the PICO population. There is, however, promising evidence of fewer harms in paediatric patients treated with PBT. There are many ongoing trials that may assist in addressing issues of comparative safety and efficacy.

- The resulting economic evaluation was a cost consequences approach, since comparative effectiveness could not be substantiated. The estimates of patients eligible for PBT is a rather small PICO defined population of 1,968. The number of patients that would potentially benefit from a reduction of adverse events compared to conventional therapy is quite small, as is the cost of these events.

- The operating cost associated with PBT is roughly 1.5 to 2.5 times higher than conventional therapy in cost comparisons reported from other countries. The adoption of PBT has the potential of expanding the expenditure for radiation by $45.8 million should it cost 2 times more than photon radiotherapy (PRT), a reasonable percentage on the international platform.

ASSESSMENT OF PROTON BEAM THERAPY (PBT)

This contracted assessment examines the evidence available for Proton Beam Therapy (PBT), a type of particle therapy. The service would be exclusively used in the purpose built proton beam facilities for the treatment of paediatric, ocular tumours and craniospinal malignancies. The target population are people with rare cancers who are currently eligible under the Medical Treatment Overseas (MTO) Program. Public funding of the technology in the target population and setting will assist patients to access curative or salvage treatment of rare cancers in Australia.

This contracted assessment of PBT addresses most of the PICO[1] elements that were pre-specified in the PICO Confirmation document that was ratified by the PICO Advisory Sub-Committee (PASC).

PROPOSED MEDICAL SERVICE

PBT is a form of external beam radiation therapy (EBRT) that utilises heavier particles (protons) instead of X-rays or gamma rays used in conventional PRT. Theoretically, the benefits of PBT over conventional PRT include improved dose distribution to tumours, reduced radiation dose and hence sparing of healthy tissues.

PBT may be used as primary treatment or as salvage therapy (in the case of recurrent disease or after failure of initial therapy). PBT is typically delivered on an outpatient basis in daily fractions. The total duration of the treatment course varies by type and location of the tumour and is usually five to eight weeks. PBT may be used as monotherapy or as a 'boost' mechanism to conventional PRT or as multi-modal treatment. The selected co-administered intervention depends upon the cancer or tumour diagnosis, underlying disease pathology, cancer staging, patient genetic risk and other characteristics.

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

POPULATION

Particle therapy technology is considered beneficial for paediatric, and young adult patients, and in patients with tumours located near vital organs or tissues. The proposed population includes patients who are currently eligible to receive PBT under the Australian Government funded MTO program. There is widespread international adoption and use of PBT for the treatment of a range of difficult to treat paediatric tumours, and tumours of the skull base, head/neck and central nervous system (CNS), with considerable ongoing international research into effectiveness in other malignancies.

COMPARATOR DETAILS

Potential comparators include conventional photon radiation therapy (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. Surgical resection may be conducted prior or post PBT therapy depending on the location and size of the tumour. Similarly, chemotherapy may be initiated as neo-adjuvant or post-adjuvant treatment with varied

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[1] Population, Intervention, Comparator, Outcomes

regimens depending on the aggressiveness of the neoplasm and the patient's Eastern Cooperative Oncology Group (ECOG) performance status.

CLINICAL MANAGEMENT ALGORITHM(S)

PBT is of particular interest in treating tumours deriving from craniospinal and ocular locations where conventional 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 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.

The clinical management algorithm is displayed in Figure 4.

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

A new facility for the delivery of PBT will need to be built, and staffed In Australia. The MTO program will no longer be needed to transport patients overseas for PBT.

CLINICAL CLAIM

The clinical claim from the PICO is that PBT is superior in clinical effectiveness and either non-inferior or superior in safety to usual standard of care. The corresponding economic evaluations should be a cost-utility or a cost-effectiveness analysis. Even though in the PICO Confirmation, the claim was superior clinical effectiveness and either non-inferior or superior in safety, the review of current evidence did not reveal these results. There is insufficient evidence of high quality to support this claim. The evidence review documents substantial uncertainty as regards to this claim. Therefore, the resulting economic evaluation was a cost consequences approach, since comparative effectiveness could not be substantiated.

APPROACH TAKEN TO THE EVIDENCE ASSESSMENT

A systematic review of published literature was undertaken to answer the research question:

Is PBT safer and more effective than alternative cancer therapies?

Publications on the use of PBT for specific PICO-defined oncology populations were identified from various databases, including Embase, Medline, the Cochrane Library, ClinicalTrials.gov and PubMed. These database searches were periodically conducted between July and September 2017.

Overall, 2959 records were initially identified. After the screening and selection of studies, five systematic reviews (SRs), two previous Health Technology Assessment (HTA) reports, and 17 comparative cohort studies were collected and comprised the evidence base for clinical evaluation of PBT. No completed RCTs fit the inclusion criteria for this evaluation.

There were major concerns with the lack of quality clinical data covering the use of PBT on nephroblastoma patients, adults with adenoid cystic carcinomas of the lacrimal or salivary glands, and soft tissue sarcomas in close proximity to the axial skeleton, for instance, rhabdomyosarcomas. There were also no comparative cohort studies examining the safety and efficacy of PBT against a non-treated study arm of cancer patients, most likely due to ethical concerns.

The evidence base for the clinical evaluation of this assessment report was largely comprised of 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.

Table 1 and Table 2 outline key characteristics of each study included in the evidence base.

RESULTS

Safety

Based on clinical findings from recently published comparative studies, PBT did not offer major safety advantages over other cancer therapies for brain tumours, spinal/paraspinal sarcomas, and ocular melanomas. There was insufficient evidence to determine the safety benefits of PBT for nephroblastomas and paraspinal soft tissue sarcomas. Conversely, PBT was found to be superior over photon-based radiotherapy alternatives for paediatric cases of cancers of the CNS, specifically in sparing in-field OARs and in lower incidence rates of endocrinopathies, haematological radiation-induced side effects, and secondary malignancies.

Effectiveness

Overall, PBT was not found to substantially improve upon the benefits of alternative cancer therapies against craniospinal tumours, soft tissue sarcomas near the axial skeleton, ocular melanomas, paediatric CNS tumours, neuroblastomas and retinoblastomas. For nephroblastomas and adenoid cystic carcinomas, high quality evidence was lacking in the determination of PBT effectiveness over its main comparator of interest, PRT.

A summary of findings is shown in Table 1.

Table 1   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	0	NA – no evidence identified	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.

Translation issue	Comments
Applicability issues	
Population and circumstances of use	The quality of the overall clinical evidence is low, mostly consisting of level III evidence. Patient characteristics in the studies have often not been uniformly well defined across all studies. The clinical evidence base has included populations from the United States, Europe and Asia, often in single centres.
	It has not been possible to pool or use meta-analysis for outcomes due to the potential use of the same patient datasets, particularly of historical records, by multiple studies, and lack of exchangeability of the PBT clinical evidence, including efficacy and safety, in the PICO populations.
	The heterogeneity of the clinical evidence is high within individual studies due to data being collected retrospectively. Not only is the risk of bias high, patient differences in characteristics, and collections from different time periods has resulted in variable outcome measures and dosage fractions between studies. The results are therefore not generalisable to the Australian population.
	There is a scarcity of publications that directly compare PBT with relevant alternative therapies including IMRT in the population that would be eligible for public funding under the proposed listing. Nonetheless, the link between the population of the requested listing and the economic model presented in Section D is discussed.
Extrapolation issues	
Progression free survival Overall survival & local recurrence rates	The low quality clinical evidence, and high risk of bias has made it difficult to draw conclusions regarding overall survival, progression rates and local recurrence rates. Further complication results from clinical outcomes reported for multiple populations in the survival evidence. Published health economic models that have assessed the cost effectiveness of PBT have sourced data from low level clinical evidence or literature based assumptions relating to alterative modalities.
Secondary malignancies	Limited information is available for secondary malignancies for patients in the PICO population.
Adverse events	While PBT may be considered superior in minimising adverse side effects, the clinical values have not been demonstrated from the increasing number of patients treated with PBT. Limited comparative long term safety information is available for PBT in the PICO population.
Transformation issues	
Utility weights applied to the economic model	Comparative health-related quality of life data is limited for PBT. In addition, the Paediatric Quality of Life instrument cannot be mapped to the utilities in the paediatric PICO population.
Healthcare resource use and associated costs	Evidence on costs relating to particle therapy and on treatment lengths relevant for Australian patients is limited

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. A probabilistic model was not used. The estimates of the cost and adverse events were based on an estimate of the demand for PBT in the tumour groups outlined in the PICO.

Table 2   Summary of the economic evaluation

Perspective	Payer
Comparator	Photon-based radiation therapy
Type of economic evaluation	
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.

Conclusions from 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 cost-effectiveness analyses reviewed lack credibility, due to the assumptions used to attempt to compensate for limited data on comparative effectiveness.

- The operating cost associated with PBT 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 total medical direct yearly expenditure on the PBT eligible PICO population, with a range of PBT MBS fees 150% to 250% of PRT, would cost between $69.4 and $92.8 million. The adoption of PBT has the potential of expanding the expenditure for radiation by $35.5 million should it be priced at three times that of PRT, a reasonable percentage in an international perspective.

- The estimate of demand for particle radiation showed that there are an estimated 58 children per year that could potentially benefit from PBT, and they are not candidates for conventional therapy. The number, and prognosis of these patients should be investigated further, and the cost and benefit of PBT treatment should be assessed.

ESTIMATED EXTENT OF USE AND FINANCIAL IMPLICATIONS

The financial implications, if public funding was via the MBS, resulting from the proposed listing of PBT are summarised in **Table 3**, which lists the number and costs of PBT services that are eligible over the next five years.

Table 3   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.

CONSUMER IMPACT SUMMARY

The following summarises the consumer issues and policy impacts identified. Consumer issues with:

- **Proposed population.** There is a risk that patients currently eligible for financial assistance under MTO program will no longer meet MTO Program 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, 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 radiotherapy supported by MSAC, including IMRT. Evidence of the effectiveness of PBT is difficult to access due to the limited number of RCTs. Appropriate scientific and clinical research on PBT may be further required to inform decisions on introducing and financing PBT technology in Australia.

- **Proposed economic analysis.** PBT will require additional operational planning of increased paediatrics, anaesthetics and post treatment services i.e. occupational therapists and speech pathologists. Patient out-of-pocket expenses may arise due to travel costs. We can assume that the MBS fee for PBT will be high due to increasing consumer interest in PBT technology and the interest in establishing PBT facilities. Demand for PBT is difficult to estimate and project.

- **Clinical management.** There is currently limited clinical expertise on 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.

ACRONYMS AND ABBREVIATIONS

Acronym/abbreviation	Meaning
ABS	Australian Bureau of Statistics
ACPSEM	Australasian College of Physical Scientists and Engineers in Medicine
AE	Adverse events
ANOVA	Analysis of variance model software
ANSTO	Australian Nuclear Science and Technology Organisation
ANZSNM	Australian New Zealand Society of Nuclear Medicine
ARTG	Australian Register of Therapeutic Goods
CADTH	Canadian Agency for Drugs and Technologies in Health
CE	Cost-effectiveness
CIT	Carbon ion therapy
CNS	Central Nervous System
CNSA	Cancer Nurses Society of Australia
CRT	Cranial radiation therapy
CT	Computed tomography
DPMQ	Dispensed Price per Maximum Quantity
EBRT	External beam radiation therapy
ECOG	Eastern Cooperative Oncology Group
GHD	Growth hormone deficiency
HDR	High dose rate
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
HU	Hounsfield units
ICER	incremental cost-effectiveness ratio

Acronym/abbreviation	Meaning
IGRT	Image guided Radiation Therapy
ILPMT	Intensity lateral proton modulated therapy
IMPT	Intensity modulated proton therapy
IMRT	Intensity modulated radiation therapy
IQ	Intelligence quotient
LDR	Low dose rate
LET	Linear energy transfer
LINAC	Linear accelerators
MBS	Medicare Benefits Schedule
MDT	Multidisciplinary team
MGH	Massachusetts General Hospital
MRI	Magnetic resonance imaging
MSAC	Medical Services Advisory Committee
MTO	Medical Treatment Overseas
MTOP	Medical Treatment Overseas Program
NCI	National Cancer Institute
NHMRC	National Health and Medical Research Council
NHS	National Health Service
NSCLC	Non-Small Cell Lung Cancer
NTCP	Normal tissue complication probability
OAR	Organs at risk
PASC	PICO Confirmation Advisory Sub-Committee of the MSAC
PBS	Pharmaceutical Benefits Scheme
PBT	Proton Beam Therapy
PET	Positron emission tomography
PICO	Patient intervention comparator outcomes

Acronym/abbreviation	Meaning
PPR	Parent-proxy report
PRT	Photon radiation therapy
PTV	Planning target volume
QALY	Quality adjusted life years
RANZCR	Royal Australian and New Zealand College of Radiologists
RBE	Relative biological effectiveness
RCT	Randomised controlled trials
ROHPG	Radiation Oncology Health Program Grants
RPC	Radiological Physics Centre
RT	Radiation therapists
RTOG	Radiation Therapy Oncology Group
SBRT	Stereotactic body radiation therapy
SEER	Surveillance, Epidemiology and End Results
SFUD	Single-field uniform dose
SOBP	Spread-out Bragg Peak
SR	Systematic review
TGA	Therapeutic Goods Administration
TPS	Treatment planning system
UK	United Kingdom
VCCC	Victorian Comprehensive Cancer Centre

SECTION A   CONTEXT

This Contracted Assessment of PBT for the treatment of paediatric, ocular tumours and craniospinal malignancies is intended for the Medical Services Advisory Committee (MSAC). MSAC evaluates new and existing health technologies and procedures for which public funding is sought in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

HealthConsult has been commissioned by the Australian Government Department of Health to conduct a systematic literature review and economic evaluation of patients who are currently eligible to receive PBT under the Australian Government funded Medical Treatment Overseas (MTO) Program. This assessment has been undertaken in order to inform MSAC's decision making regarding whether the proposed medical service for PBT should be publicly funded for the curative or salvage treatment of rare cancers outlined in the PICO population.

Appendix A provides a list of the people involved in the development of this Assessment Report.

A.1.   ITEMS IN THE AGREED PICO CONFIRMATION

This Contracted Assessment of PBT for the treatment of paediatric tumours, ocular tumours and craniospinal malignancies addresses most of the PICO elements that were pre-specified in the PICO Confirmation submitted to PASC.

First, in the patient component, no information on comparative effectiveness of PBT was found in the rhabdomyosoma or nephroblastoma categories. Second, in the comparator component, there is no information provided in the "no treatment alternative" category. In the outcomes component, disease progression is not dealt with per se, but tumour recurrence, secondary malignancy, and freedom from malignancy was reported in the literature reviewed, and these can be considered as forms of disease progression outcomes. And, finally, in the safety component, secondary malignancy was treated as an outcome measure in much of the literature reviewed.

The proposed use of PBT in Australian clinical practice in the MTO population was outlined in a PICO Confirmation that was presented to, and accepted by, the PASC in April 2017. The PICO Confirmation was released for public comment in May 2017.

This Contracted Assessment includes information relating to international HTAs of patients treated in the PICO population, ongoing clinical trials of relevance, and important factors relevant to dose comparison planning.

A.2.   PROPOSED MEDICAL SERVICE

Treatment of neoplasms and non-malignant tumours involves various treatment modalities based on the underlying pathogenesis of the condition and individual patient characteristics. Chemotherapy, surgery, immunotherapy and radiation therapy are commonly used as standard treatment with curative or salvage intent**.** Paediatric and craniospinal malignancies are often difficult to treat due to the requirement to manage overall toxicities and their proximity to essential organs.

The goal of radiotherapy is to achieve sufficient target coverage while sparing normal tissue. PBT is a form of EBRT that uses heavier particles (protons) instead of photons used in conventional photon radiotherapy (PRT). Theoretically, the principle benefit of PBT over conventional PRT is the superior radiation dose distribution. This enables a more conformal dose of radiation to be delivered to the tumour while sparing more of the surrounding healthy tissue.

Traditional radiotherapy treatment is either administered via EBRT or brachytherapy. Brachytherapy delivers radiation from a small radioactive source, or seed, implanted directly into or next to the tumour which emits photons. There are two main types of brachytherapy: low dose rate (LDR) and high dose rate (HDR). LDR brachytherapy involves the small radioactive 'seeds' being permanently implanted near or in the tumour, most commonly used for low risk prostate cancer, while HDR brachytherapy involves the removal of the seed after each treatment session. Plaque brachytherapy is a type of HDR brachytherapy to treat eye tumours. Brachytherapy can be used in conjunction with EBRT.

Advanced EBRT techniques to minimise radiation to the normal tissue are:

- IMRT where size and shape of the radiation field is varied throughout the treatment session

- Image guided Radiation Therapy (IGRT) which guides radiotherapy with imaging in each treatment session.

Currently radiotherapy facilities in Australia use EBRT (most commonly photons, though also electrons for superficial treatment) and brachytherapy. For PRT, photon radiation dose, as a function of depth in the patient, rises initially as the electrons ejected by photons build up to a maximum and then declines exponentially as photons are absorbed. For EBRT, a photon beam deposits dose from entry all the way to where it exits the body, thus potentially increasing the risk of secondary malignancies.

PBT may be used as primary treatment or as salvage therapy (in the case of recurrent disease or after failure of initial therapy). PBT is typically delivered on an outpatient basis in daily fractions, with each treatment session taking 15-60 minutes depending on the type and location of the tumour[2]. The total duration of the treatment course varies by type and location of the tumour and may last up to eight weeks.

PBT may be used as monotherapy or as a 'boost' mechanism to conventional PRT or as multi-modal treatment (i.e. PBT plus adjuvant chemotherapy, or PBT plus surgery)[2]. The selected co-administered interventions depend upon the cancer or tumour diagnosis, underlying disease pathology, cancer staging, patient genetic risk and other characteristics. Surgical resection options are based on tumour proximity to organs and location of surgery. Post PBT treatment options may be considered in order to reduce or manage the impacts of radiation toxicity.

PBT is particularly sensitive to patient movement during application, whereby small patient movements can result in the actual administered dose varying from the planned dose. Anaesthetics can be co-administered with PBT to restrict patient mobility. The expected use of anaesthetics is likely to be high in the paediatric population. Anti-nausea medication may also be administered for symptom control, although this is expected to be less than conventional PRT.

Traditionally, PBT has been delivered via passively scattered beam technology, typically using a fixed beam. However, newer proton delivery systems use pencil scanning technology which allows intensity modulated proton therapy (IMPT).

All forms of radiation therapy involve a multidisciplinary team (MDT) including radiation oncologists, medical physicists and radiation therapists. Some site-specific cancers may also involve a diagnostic radiologist and/or surgeon. Prior to radiation therapy, patients will have undergone diagnostic imaging and pathology, and, in some cases, may have had surgery or other treatment such as chemotherapy. There is no difference between the different occupations required for the MDT, nor the requirement for diagnostic testing between conventional radiation therapy and PBT.

Additional allied health post-treatment services including occupational therapists and speech pathologists may also be required. Refer to Section A.4 for further information of associated interventions by cancer type.

CHARACTERISTICS OF PROTONS

William Bragg discovered the deposition of ionisation density at the end of the path of alpha particles in 1905. The 'Bragg curve'—a depth dose curve—plots the energy deposition of ionising radiation (including protons, photons and electrons) as it travels through matter, as shown in Figure 1. The point of highest dose is called the Bragg peak.

Figure 1   Typical Bragg Curve for electrons, photons and protons

Source: https://physics.stackexchange.com/questions/169665/dose-depth-curve-of-photons-vs-protons
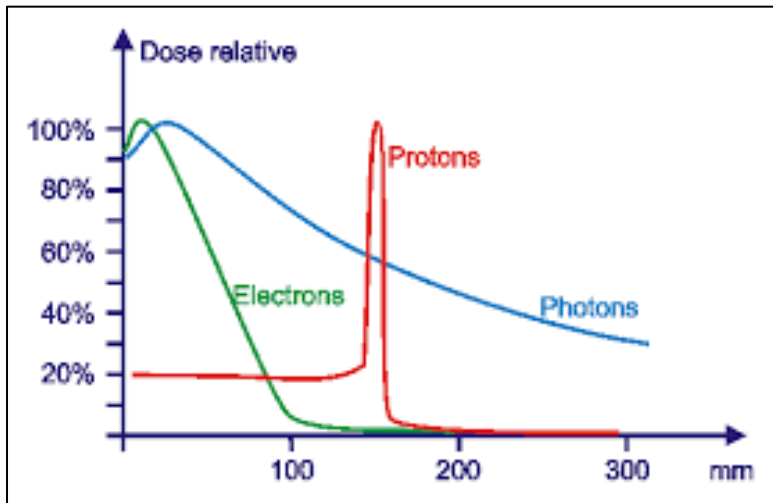
In contrast to photons, when protons of a given energy (typically in the range of 70 to 250 MeV) penetrate matter, they slow down continuously as a function of depth. The rate of their energy loss increases with decreasing velocity. This continues until their entire energy is depleted and then they come to an abrupt stop. The depth of the peak, the range of protons, is a function of the initial energy. The total radiation dosage of the protons is known as the Spread-out Bragg Peak (SOBP).

Figure 2 compares the depth dose curves for 15 MV photons and a proton SOBP. The figure depicts a target volume and ideal dose distribution for the target volume with zero dose outside the target volume. Notably, the proton dose distribution approaches the ideal case greater than the photon dose distribution. In theory, the dose deposited beyond the range is negligible. As protons traverse a medium, they also scatter laterally, but the dose outside the boundary of a beam of protons falls rapidly. Narrow, monoenergetic beams of protons for therapeutic use can be produced and spread longitudinally.

Figure 2   Comparison between the depth dose curves for 15 MV photons and a proton spread-out Bragg peak (SOBP)
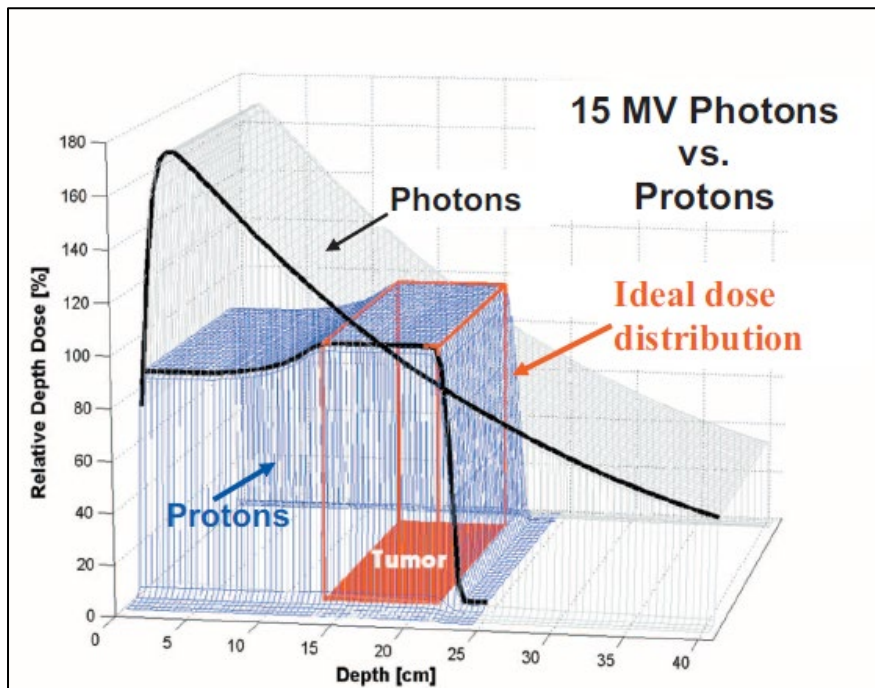
Source: Smith 2009 p557 Figure 1 [3]

Photons and protons both have a low density of ionisation events or linear energy transfer (LET). Based on numerous in vitro and animal experiments, protons have been assumed to have a 10% higher biological effectiveness relative to photons on both healthy and cancerous tissue. In clinical practice, the physical dose, in units of Gray (Gy), delivered by protons is multiplied by 1.1 to obtain the relative biological effectiveness dose (RBE) in units of Gy.

The potential benefits of proton therapy are a consequence of normal tissues around the target (tumour) receiving very little radiation dose [4]. In the treatment process, the dose to healthy cells is reduced by factors between 3 and 10. This is particularly important in the treatment of children who have many years of life before them.

PBT PLANNING AND TREATMENT

PBT allows for radiation treatment plans that are highly conformal to the target volume delivered. PBT planning defines the necessary field sizes, gantry angles, and beam energies needed to achieve the desired radiation dose distribution. PBT treatment planning is a multi-step process and shares functions common to other forms of EBRT planning.

(1)   **Simulation and imaging**: Three dimensional acquisition of the target region by simulation employing magnetic resonance imaging (MRI) or computed tomography (CT), with or without positron emission tomography (PET) is an essential prerequisite to PBT treatment planning. If respiratory or other organ movement is expected, multi-phasic treatment planning images may be ordered to account for motion when rendering target volumes.

(2)   **Contouring**: The radiation oncologist defines a margin around the Gross Tumour Volume (if there has not been previous treatment with surgery or chemotherapy), the Clinical Target Volume (which encompasses the areas at risk for microscopic disease) and nearby normal structures that could potentially be harmed by radiation.

(3)   **Radiation dose prescribing**: Specific dose coverage requirements are assigned by the radiation oncologist for the Clinical Target Volume to maximise the potential for disease control and minimise the risk of radiation injury to normal tissue.

(4)   **Dosimetric planning and calculations**: In Australia, routine dosimetric planning is performed by a radiation therapist who calculates a treatment plan to deliver the prescribed radiation dose to the Clinical Target Volume while simultaneously satisfying normal tissue constraints. The treatment plan specifies all delivery parameters and/or field specific hardware as well as the expected dose distribution. After completion of isodose planning, an independent verification of the radiation dose should be performed by a medical physicist. As PBT dose distributions are sensitive to changes in target depth and shape, changes in patient anatomy during treatment may require repeat planning.

(5)   **Patient specific verification:** An independent dose calculation measurement is conducted to confirm whether the intended dose distribution for the patient is physically verifiable or feasible. Proton planning is complex and the differences between proton and photon plans is further explored in Section A.7.

PBT DELIVERY METHODS

To produce protons, negatively charged electrons are split from hydrogen atoms leaving the positively charged protons, which are accelerated to 40 to 70% of the speed of light, then directed through a magnetic beam steering system to the treatment room.

Proton beams are generated either in a cyclotron which uses a single-stage acceleration process (i.e. the cyclotron alone can accelerate the protons to the required energies), or a synchrotron, with subsequent delivery through high vacuum 'beamline' structures to treatment rooms.

Within the treatment room, the proton beam can then be guided to deliver therapy beams via gantries, allowing 360 degrees rotation at an optimal combination of angles, to the patient. Commercial Cyclotrons (protons only) are different to a synchrotron, with each system having their own set advantages and disadvantages. Thus, studies that use different PBT approaches may not be directly comparable.

The delivery methods of the proton beam fall into two general categories: *passive scattering* and *pencil beam scanning*. Centres may include a hybrid of PBT technologies.

In *pencil beam scanning* or spot scanning delivery method, radiation dose distribution inside the patient is controlled by scanning magnets instead of the beam-shaping hardware such as the scatterer

or the collimator. An important difference of pencil beam scanning compared to passive scattering is that it allows for intensity lateral proton modulated therapy (ILPMT). The weights of the beams can be reduced to lower the dose at the organ at risk and a beam from another direction can be used for dose compensation[5]. The use of controlled magnets results in only a small deviation in the trajectory of the proton beam as it enters the human body enabling targeting of tumours very close to critical organs. Tumours that are resistant to normal electromagnetic radiation may also be killed.

Table 4 describes methods of producing a clinical proton beam to treat entire target volume and methods of achieving adequate dose distributions.

Table 4   Methods of producing a clinical proton beam and achieving adequate dose distributions

Methods of producing a clinical proton beam to treat entire target volume	
Passive scattering	Works on the principle that high atomic number materials, such as lead, scatter the beam with minimum energy loss and low atomic number materials, such as plastic, decrease proton energy with minimum scatter. Combining these materials to produce patient specific collimators and compensators results in a conformal treatment beam with a SOBP.
Uniform scanning	This is similar to passive scattering with the difference that the beam is spread in the lateral direction through magnetically deflecting the beam with constant fluency instead of using a scattering foil. Different spot weights are produced using a compensator, as in passive scattering.
Active scanning	This uses magnetic fields to deflect the path of each proton beam towards the planned position in the target volume. Individual Bragg peaks are distributed within the target volume and the cumulative effect produces an effective SOBP without the need for compensators. This is achieved by either continuous magnetic scanning or spot scanning. The latter is analogous to the step-and-shoot mode in IMRT (i.e. a non-continuous delivery of dose, where the exact position is determined before the dose is delivered).
Methods of achieving adequate dose distributions	
Single-field uniform dose (SFUD)	Single individually optimised proton fields that each deliver a homogeneous dose to a volume. If necessary, these can be combined by simple addition.
Field patching	The sharp distal edge dose gradient can be matched up to the lateral edges of another "patch" field to produce a continuous dose distribution. Where possible, equivalent opposite fields are also used to reduce the potential for dose variation at the abutting edges. Multiple fields in patch work can be used to achieve multiple dose gradients inside a treatment volume. Field patching is a 3D extension of matching lateral field edges. Therefore, if multiple fields are used, each one can deliver a homogeneous dose to part of the volume.
Intensity modulated proton therapy (IMPT)	IMPT is analogous to IMRT, and is a mode of treatment delivery achievable only with active scanning beams. IMPT uses narrow proton beams which are magnetically moved over the volume in the transverse plane while the energy and intensity are altered to control dose to a point and sculpt the dose at depth. Unlike SFUD treatments, IMPT can deliver a number of non-uniform fields to produce the desired dose distribution.

Abbreviations: SOBP, Spread-out Bragg Peak; IMRT, Intensity modulated radiation therapy; IMPT, Intensity modulated proton therapy; SFUD, Single-field uniform dose; 3D, three dimensional.

PBT FACILITIES

There has been a marked increase in investment in particle therapy within the past two decades. As at January 2017, throughout the world there were sixty-six particle centres in operation (proton, carbon and combined proton/carbon), and sixty-one centres either planned or under construction. Data collected by the Particle Therapy Co-Operative Group indicate that over 130,000 patients have been treated with proton therapy between 1954 and 2015. The majority of proton facilities are located in the United States, Japan, China and Europe.

There are currently ten carbon ion, or combined carbon ion/proton facilities established in Japan, Germany, Italy and China, and four with additional facilities either under construction or planned in Austria, China, South Korea and the United States. Since the mid-1990's, there has been interest in the potential establishment of an Australian particle therapy centre.

The first Australian PBT facility is anticipated to be operational in Adelaide by 2020. Table 5 presents the Australian States that are planning the development of particle therapy facilities. It is anticipated in PBT centres developed in Australia will be based on synchrotron technology and the methods for achieving adequate dose distributions will utilise IMPT (Advice from clinical experts August 2017).

Table 5   Planned Particle Therapy Centres within Australia

State	Description
South Australia	The Australian Bragg Centre for Proton Therapy and Research (SAHMRI) in South Australia is planning to build a proton beam facility (synchrotron, two gantries and one fixed beam) in Adelaide. In the 2017 Commonwealth Budget, the Government allocated $68 million towards the capital development of the SAHMRI PBT facility. It is envisaged that the SAHMRI PBT treatment centre will become operational by 2020. Over the past 5 years South Australia has developed a highly experienced team with the necessary expertise. International collaboration will continue through the operational phase with research partnerships.
Victoria	As part of the 2015-2016 Victorian State budget, the Government announced $2 million funding to progress planning and development of a National Centre for PBT as part of the Victorian Comprehensive Cancer Centre (VCCC), undertaken in conjunction with the University of Melbourne and Peter MacCallum Cancer Centre. Subsequently, in August 2016, the Victorian Government announced $50 million for further planning activity, with Parkville nominated as a potential PBT location.
Queensland	Queensland (public) – the Queensland Metro North Hospital and Health Service have developed a business plan for the potential introduction of a PBT facility at the Royal Brisbane and Women's Hospital. It is proposed that this facility will be developed in partnership with the University of Queensland, the Queensland Institute of Technology, and Children's Health Queensland.
	Queensland (private) - in September 2014, Mater Health Services announced an alliance with Proton Therapy Australia Pty Ltd to construct a $170 million proton beam facility,54 and as at October 2016 were seeking equity for land purchase near the Lady Cilento Children's Hospital, South Brisbane.

State	Description
NSW	Westmead Hospital, in conjunction with the University of Sydney and the University of Wollongong have developed a business case for a National Particle Therapy and Research Centre (using carbon ions and protons) to be located at the Westmead Hospital precinct.

Source: HealthPACT 2017 Report[6]
Abbreviations: SAHMRI, The Australian Bragg Centre for Proton Therapy and Research; PBT, proton beam therapy; VCCC, Victorian Comprehensive Cancer Centre.

Given that plans to build PBT centres are ongoing, HealthPACT 2017 recommended consideration to form a high-level national reference group with appropriate government, clinical and scientific input. The role of this entity would be to oversee the potential introduction of this technology into the healthcare systems of Australia and New Zealand. Currently, relevant entities involved in the proposed NSW, QLD and SA facilities have formalised Memorandums of Understanding to network and integrate their planning activities. This clinician-led collaboration has established links with Australian Nuclear Science and Technology Organisation (ANSTO) and Royal Australian and New Zealand College of Radiologists (RANZCR); and internationally with the New Zealand Government, the Queen's Medical Research Institute (UK), the European Organisation for Nuclear Research (CERN), and with particle centres in the USA, Germany, Denmark, Italy and Japan.

MARKETING STATUS OF DEVICE AND TECHNOLOGY

The Food and Drug Administration in the USA does not regulate radiation therapy, since it is considered a procedure. However, the accelerators and other equipment used to generate and deliver PBT are regulated by the FDA.

In Australia, all therapeutic devices marketed require inclusion on the Australian Register of Therapeutic Goods (ARTG). The items on the ARTG that are relevant to this Assessment Report are shown in Table 6. Two companies have registered 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. A diagnostic imager suitable for proton therapy has also been registered by one company.

Table 6   Proton Beam Therapy devices included on the ARTG

ARTG no.	Product no.	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	Proton Therapy Australia Pty Ltd.
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	Medical Device Class IIb	Proton Therapy Australia Pty Ltd.

ARTG no.	Product no.	Product description	Product category	Sponsor
		equipment and to provide correction feedback to the radiation therapy device.		
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	Varian Medical Systems Australasia Pty Ltd.

Source: Therapeutic Goods Administration, accessed 20th July 2017 Link to TGA.gov.au
Abbreviations: ARTG no, Australian Register of Therapeutic Goods Number

PBT is complex non-invasive technology with long-term safety implications classified as medium to high risk by the TGA (Class IIB). HealthPACT recommends that management of PBT facilities will also require accreditation and credentialing of staff. Refer to Section F for discussion of these additional requirements.

OTHER INDICATIONS

While PBT is only being considered in this contracted assessment for the treatment of a range of paediatric and craniospinal malignancies as defined in the PICO, the technology is being used elsewhere to treat a broader range of neoplasms. Particle therapy may be the only viable treatment option for patients where a tumour cannot be resected with appropriate margins due to proximity to critical structures, and where, with conventional PRT there is an inability to irradiate to a curative dose without overdosing local critical structures. Inclusion of individual comparative plan assessment within the proposed medical service would allow for evolving clinical evidence for conditions inside and outside the PICO population. Refer to Section A.7 for further information relating to comparative planning.

The financial implications of use beyond the PICO population are further explored in Section E. This report focuses on the effectiveness and costs associated with PBT for a population outlined in the list of indications in the PICO, and thus does not involve the analysis of the investment decision for PBT infrastructure.

CURRENT FUNDING ARRANGEMENTS

Current funding for PBT services is provided under the MTO Program. The MTO Program provides financial assistance for Australians with a life threatening condition to receive life-saving medical treatment overseas where effective treatment is not available in Australia. To be eligible for the Program, the patient must meet the four mandatory medical criteria (as assessed by a panel of Departmental Medical Advisers) and their application must be supported by the treating Australian specialist and the Faculty of Radiation Oncology. It is the treating Australian specialist that nominates where their patient would be best treated.

The indications for PBT under the MTO Program have included clival chordoma, spinal thoracic chordoma, atypical teratoid rhabdoid tumour, craniopharyngioma, pelvic osteosarcoma, supratentorial anaplastic ependymoma, skull base chondrosarcoma, chondrosarcoma of the cervical spine, perimeningeal rhabdomyosarcoma, adenoid cystic carcinoma on the lacrimal gland and ocular melanoma.

Since the inception of the MTO Program in 1995, there has been <redacted> applicants for PBT from 1998 to 2016 (<redacted>applications approved, <redacted> applications rejected, <redacted> application withdrawn, and <redacted> are currently under assessment). The overall number of patients approved for overseas PBT therapy has been small. The number of patients that received financial assistance in the last five years include: <redacted> patients in 2012, <redacted> patients in 2013, <redacted> patients in 2014, <redacted>patients in 2015, and <redacted> patients in 2016. The assessment process takes a minimum of six weeks.

Patients who received PBT overseas ranged in age from <redacted> to <redacted> years old. For the 2015/16 financial year, the overall fees paid by the MTO Program were <redacted>(<redacted> cases) at an average price of $<redacted>per case. In reaction to a question on the PBT in the MTO, the department of health reported that in the period 2012-2014 the MTO Program has funded <redacted> patients to obtain PBT at various centres overseas at a total cost of AU$<redacted>. This equates to an average cost of around AU$<redacted>per patient.

The overall costs to MTOP for financial years 2014/15 and 2015/16 is provided below:

-   2014/15: $<redacted> (<redacted> cases) at an average of $<redacted> per case

-   2015/16: $<redacted> (<redacted> cases) at an average of $<redacted> per case

The costs include medical direct costs, transportation, accommodation, hospitalisation, and cost for an attending physician for a six to eight week course of treatment. The data reflect <redacted> patients per year being sent overseas for PBT. The Assessment team was not provided with details of the outcomes of the treatment which are not known to the MTOP, nor the tumour type.

Once PBT facilities are operational in Australia, there is a risk that patients currently eligible for financial assistance under the MTO Program will no longer be eligible for reimbursement of their treatment costs as they will no longer meet the mandatory MTO eligibility criteria. And if there is no MBS listing for PBT services, eligible patients currently accessing the MTO Program may consequently be required to pay the entire cost of PBT. This raises issues in terms of service funding, reimbursement, patient affordability and equitable patient access to treatment.

However, reliance on overseas PBT facilities has a number of additional challenges impacting equitable patient access. Redacted.

Populations included in international reimbursement arrangements

PBT has been adopted worldwide for the treatment of a range of difficult to treat paediatric tumours, and tumours of the skull base, head/neck and central nervous system. Similar to Australia, a number of countries refer patients overseas for PBT including Canada and the UK. Populations by which overseas countries have reimbursement arrangements in place for PBT services were identified by searching relevant databases maintained by HTA agencies and a grey literature search. Relevant HTA reports that have included an evidence-based review of PBT technology are summarised in Section A.4.

Table 7 Populations for which overseas countries reimburse for access to overseas PBT

Country	Review of evidence	Description of HTA recommendations
United States[7]	High quality systematic literature search completed in 2014. Refer to Section B for further information.	PBT is a covered benefit with conditions consistent with the criteria identified in the reimbursement determination including: ocular cancers, paediatric cancers (e.g., medulloblastoma, retinoblastoma, Ewing sarcoma), central nervous system cancers (e.g. brain, spinal, paraspinal tumours). Other conditions: patient has had prior radiation in the expected treatment field with contraindication to all other forms of therapy.
United States (Oregan State)	Moderate quality systematic literature search completed. Washington State literature reviewed considered in final recommendations.	PBT is recommended for coverage for malignant ocular tumours (strong recommendation). PBT is recommended for coverage (weak recommendation) for: malignant brain, spinal, skull base, paranasal sinus, and juxta spinal tumours, paediatric malignant tumours (incident cancer under age 21). PBT is not recommended for coverage for cancer of the bone, breast, oropharynx, nasopharynx, oesophagus, liver, lung, or prostate or for gynaecologic or gastrointestinal cancers, lymphoma, sarcoma, thymoma, seminoma, arteriovenous malformation or ocular hemangiomas (weak recommendation).
United Kingdom NHS, 2012	Systematic literature search not completed. Economic modelling based on Monte Carlo simulation of a theoretical cohort. Refer to Section C for further information.	PBT has not been evaluated by National Institute for Health and Clinical Excellence (NICE); there are very few randomised trials worldwide that include PBT. One facility is currently in operation for ocular malignancies. International modelling of PBT demand was recently undertaken within the United Kingdom (UK). As at 2012, with a population of 64 million, the UK Department of Health modelled a PBT demand of 1,487 patients (including 252 paediatric cases) per annum, utilising predominantly complex craniospinal indications. A PBT facility (comprised of three gantry treatment rooms and a research room) was anticipated to achieve a maximum throughput of 750 patients per year. The UK Government (NHS) funded construction of two PBT facilities (currently underway), with the potential development of a third facility in the longer term.
Netherlands[8]	High quality HTA assessment.	In 2009, the Health Council of Ministry of Health published the Horizon Scanning Report Proton Radiotherapy, which paved the way for the clinical introduction of proton therapy in The Netherlands. In this report, four categories of indications were identified, including: standard indications (e.g. paediatric patients), prevention of secondary tumours in young patients with favourable prognosis, potential indications (i.e. dose escalation without enhancing toxicity) and the model-based indications (i.e. prevention of side effects). The model-based indications are the largest group of indications. In this category, patients will only be selected for proton therapy after an individual planning comparison and if the difference in dose translates in a minimal difference in NTCP. The maximum capacity to be created is 2,200 patients per year, divided among these four centres. Two centres are now under construction and expected to treat patients in 2017.
Canada[9]	Alberta Health Services completed a high quality assessment. CADTH have completed a rapid fire literature review and further HTA assessments are in progress. Refer to Section B for further information.	PBT was only recently approved for use in Canada. The first system (Mevion S250) received a medical device licence in early 2015. There is one operational site in Vancouver, British Columbia (TRIUMF Proton Treatment Facility), for the treatment of ocular tumours. Alberta Health Services Cancer Care Proton Therapy Guidelines working group has recommended that highest priority for PBT be for paediatric patients, as well as adults, with chondrosarcomas or chordoma of the skull base, large uveal and mucosal melanomas, large unresectable sarcomas, renal cell carcinoma, pancreatic and liver cancers. Canadian Agency for Drugs and Technologies in Health is also known as CADTH.

Sources: Institute for clinical and economic review 2014[7], Widder et al 2016[8], Patel et al 2014[9]
Abbreviations: PBT, proton beam therapy; NICE, National Institute for Health and Clinical Excellence (United Kingdom); UK, United Kingdom; NHS, National Service (United Kingdom); NTCP, normal tissue complication probability.

A report based on twenty-one assessments from nine institutions in seven countries was conducted in 2013 by MedAustron. The authors concluded that there is a wide consensus in the United States and Europe that there is limited prospectively comparative PBT trials results available. There is no confirmed knowledge of whether the promise of theoretical advantages can be translated into patient-relevant advantages (longer survival, quality of life through fewer side effects). Only a few (priority) standard indications are valid for this assessment: paediatric tumours, spinal and paraspinal sarcomas and carcinomas, eye tumours (that are not indexed for brachytherapy), AVM/cerebral arteriovenous malformations, (some) head-neck and intracranial tumours. However, the authors noted that the scientific evidence for these tumours is not decisive or proven. The greater need for research including comparative randomised clinical trials for PBT has been recommended by a number of HTA Authorities, including the Veterans Administration and the Washington Health Care Authority in the USA.

A.3. PROPOSAL FOR PUBLIC FUNDING

On 12 April 2016, the Minister for Health wrote to the MSAC Chair requesting MSAC to consider future public funding arrangements for PBT for the limited clinical indications supported by the MTO Program. The proposed clinical management algorithm included in the PICO Confirmation assumes that PBT will be included on the MBS after facilities become operational in Australia, and will provide patients with an alternative to the existing treatments available in Australia.

A.4. PROPOSED POPULATION

As a result of both its superior depth dose distribution and reduced integral dose, particle therapy technology is considered beneficial for paediatric and young adult patients, and in patients with tumours located near vital organs or tissues. The proposed population includes patients who are currently eligible to receive PBT under the Australian Government funded MTO Program. There is widespread international adoption and use of PBT for the treatment of a range of difficult to treat paediatric tumours, and tumours of the skull base, head/neck and central nervous system, with considerable ongoing international research into effectiveness in other malignancies.

The following clinical conditions that acquired PBT services through the MTO Program are included in the PICO assessment:
- chordoma of the axial skeleton (defined as the skull, vertebral column and bony pelvis);
- sarcoma of the axial skeleton;
- paediatric CNS tumour;
- ocular melanoma;
- retinoblastoma;
- soft tissue sarcoma in close proximity to the axial skeleton (to include rhabdomyosarcoma);
- adenoid cystic carcinoma of the lacrimal or salivary glands;
- craniopharyngioma;
- intracranial germ cell tumour;
- neuroblastoma; and

- nephroblastoma.

Redacted.

PICO 1: HEAD/SKELETON TUMOURS

The head and skeleton tumours defined in the PICO are located in or around the axial skeleton (defined as the skull, spinal cord, vertebral column and bony pelvis). This includes tumours with adjacent nerves whose integrity could be compromised as a result of surgery or radiation, where a tumour cannot be resected with appropriate margins due to proximity to critical structures, and where, with conventional PRT, there is an inability to irradiate to a curative dose without overdosing other local organs.

Total surgical resection with an acceptable functional outcome is often difficult to achieve, and because of the radio sensitivity of the OARs PRT may not be an option for some patients.

Chordoma

Chordoma is a rare bone cancer that accounts for 1–4% of all bone malignancies and are considered to be derived from axial skeleton notochord remnants**.** These tumours are locally invasive, often slow growing and are rare in children. Chordoma tumours are commonly resistant to chemotherapy and PRT.

Sarcomas

Sarcomas are rare malignant tumours of bone and soft tissue. Sarcomas are cancers that originate from mesenchymal tissue, including bone, muscle, cartilage, fat and vessel cells. There are approximately 850 new cases of sarcoma each year in Australia[10]. They are a heterogeneous group of malignancies, and include many anatomical sites and subtypes. The classification of 'bone sarcoma' includes osteosarcoma, Ewing sarcoma, chondrosarcoma, malignant fibrous histiocytoma and Spindle cell sarcoma. Sarcomas have traditionally been managed by wide excisional surgery and radiotherapy; with the use of chemotherapy reserved for advanced disease.

Rhabdomyosarcoma is a soft tissue tumour that is believed to arise from primitive muscle cells. The most common sites are the head and neck (28%), extremities (24%), and genitourinary (GU) tract (18%). Other notable sites include the trunk (11%), orbit (7%), and retroperitoneum (6%). These tumours typically arise in children and young adults, and are rare in adults.

Radiotherapy is widely used as an adjunct to surgery in the management of soft tissue sarcomas as the risk of failure following surgery may be high. Radiotherapy is only occasionally employed in the management of osteosarcomas, where indications include incompletely resected or unresectable primary disease. In contrast, radiotherapy remains an integral part of multimodality treatment for Ewing sarcoma. Clinical experience suggests that sarcomas vary widely in radio sensitivity. Radiotherapy is delivered with conventional fractionation in treatment with curative intent for this

type of tumour. Intensity modulated radiotherapy (IMRT) or PBT may be appropriate when optimal dose fractionation is not achievable with conventional techniques.

Craniopharyngioma

Craniopharyngioma are slow growing benign tumours of the sellar and parasellar region. During adulthood there is a peak incidence between 40 and 44 years [11]. These tumours also occur in children and the effects of the tumour, and treatment, on children are more considerable. There are two histopathological types, the adamantinomatous and the papillary type. The latter type occurs almost exclusively in adult patients. The presenting symptoms develop over years and display a wide spectrum comprising visual, endocrine, hypothalamic, neurological, and neuropsychological manifestations. Currently, the main treatment option consist of surgical excision followed by radiation therapy in case of a residual tumour. Although the overall long-term survival is good, it is often associated with substantial morbidity. Pre-existing disorders are often permanent or even exacerbated by treatment.

Germ Cell tumours

Germ cell tumours occur when abnormal germ cells grow in an uncontrolled way. A germ cell is the type of cell that develops into oocytes (in the ovaries) or sperm (in the testicles). Germ cell tumours can develop before or after birth, and can occur in the ovaries or testicles, or in other parts of the body. This is because sometimes, when the foetus is developing in the womb, germ cells migrate to other parts of the body. Those that form in the brain or spinal column are called intracranial or intraspinal germ cell tumours, and those that form in other parts of the body are called extracranial, extragonadal germ cell tumours. Germ cell tumours that are extracranial and extragonadal tend to form along the midline of the body, such as in the sacrococcygeal region of the spine, in the retroperitoneum, in the mediastinum or in the neck. Survival data sourced from the National Cancer Institute (NCI) Surveillance, Epidemiology and End Results program (SEER) database (1992–2005) for 207 malignant nonpineal central nervous system (CNS) germ cell tumours showed 77.3% overall survival at 5 years, and 67.6% at 10 years.

PICO 2: OCULAR TUMOURS

Ocular melanoma is the second most common type of melanoma after cutaneous. It arises from melanocytes situated in the conjunctival membrane and uveal tract of the eye. Ocular melanoma may also arise from melanocytes located in the orbit. The uveal tract is the most frequent site of origin of ocular melanomas and comprises 82.5% of all of them, while conjunctival melanoma is far less common[12]. The great majority of ocular melanomas are primary. However, metastatic melanoma from primary cutaneous site can also occur in the ocular region, and it accounts for less than 5% of all metastases to the eye and orbit[12]. The observed incidence of uveal melanoma in Australia is 8 per million in men, and 6.1 per million in women. This rate is higher than international comparisons with the observed incidence rate in the United States equal to 6.8 per million in men and 5.3 per million in

women. Radiotherapy is commonly used to treat uveal melanoma with treatment modalities including brachytherapy and EBRT commonly used.

PICO 3: PAEDIATRICS AND ADOLESCENTS

Childhood cancer remains the most common cause of disease-related death among children aged 114 years old in Australia, accounting for 17% of all deaths in this age group[13]. The burden of disease to the Australian community is significant, whereby each death represents at least 65 years of life lost from normal life expectancy. Long-term distress and psychosocial problems is also associated for the families involved. Expert advice indicates that this category of patients should be extended to young adults up to, and including, 25 years of age.

Reported cancer incidence and mortality trends in Australian children have been based on the International Classification of Childhood Cancers (ICCC-3) which includes non-malignant intracranial and intraspinal tumours. Cancer incidence rates for Australian children are relatively high when compared internationally. Approximately 620 children under the age of 15 are diagnosed with cancer in Australia each year, at an average annual rate of almost 160 per million population[13]. The most common cancer diagnoses in children and adolescents are leukaemia, lymphoma and CNS neoplasms.

Mortality rates for childhood cancer in Australia are among the lowest reported in the world and overall deaths are declining. About 40% of all childhood cancer deaths were due to tumours of the CNS, followed by leukaemia (22%), neuroblastoma (11%) and soft tissue sarcomas (10%). A sharp decline of 9.4% per year was observed in mortality due to childhood leukaemia between 1998 and 2008, which have resulted from improved access to newer cost-effective chemotherapy agents. The mortality rate for neoplasms derived from the CNS has remained constant for the same period, indicating a high clinical need for the availability of effective treatments.

The Paediatric Radiation Oncology Registry commenced in 1997 to prospectively gather information about the number of children in Australia and New Zealand undergoing a course of radiation treatment under the age of 16 years. Enrolment has been voluntary, with just over 200 children under the age of three years recorded to have received radiotherapy during the period of 1999 to 2010. A greater number of children were diagnosed in this young age group, indicating radiotherapy was deferred for some children until over the age of three years. PBT is considered a beneficial treatment option for paediatric and young adult patients as a result of both its superior conformality and reduced integral dose. Patients as young as <redacted> have accessed treatment at overseas proton facilities via the MTO Program and paediatric clinical trials include infants as young as 12 months.

The additional clinical indications relevant for the paediatric and adolescent population defined in the PICO population by PASC include:

Central Nervous System

CNS neoplasms are solid tumours of the cranial cavity and frequently develop between 5 to 10 years of age. Tumours of the CNS occur most commonly in the brain and vary widely in terms of pathologic appearance, behaviour and prognosis. Astrocytomas form the most common diagnostic subgroup and were responsible for 47.7% of all childhood tumours of the CNS diagnosed in Australia during 1995-2004, followed by intracranial and intraspinal embryonal tumours (18.7%), other gliomas (11.7%) and ependymomas and choroid plexus tumours (9.2%). The remaining 12.8% were other specified, and unspecified, intracranial and intraspinal neoplasms. Both malignant and non-malignant childhood tumours of the CNS may have similar symptoms and outcomes.

Medulloblastoma is a highly malignant primary brain tumour that originates in the cerebellum or posterior fossa. It is a particularly invasive and rapidly growing tumour. It spreads through the cerebrospinal fluid and frequently metastasise to different locations in the brain and spine. Treatment begins with surgery followed by radiation therapy. Medulloblastoma is a cancer which affects young children. 40% of all cases are diagnosed in children under 5.

Retinoblastoma

Retinoblastoma occurs when abnormal cells in the retina (the light-sensing area at the back of the eye) grow in an uncontrolled way. It usually occurs in young children, and can affect one or both eyes. Retinoblastoma is more common in children under three years of age, although it can occur at any age. Retinoblastomas are due to a faulty RB1 gene. This faulty gene may be inherited, or it may develop for the first time in the child. Most cases of retinoblastoma do not run in families.

Neuroblastoma

Neuroblastoma is an extracranial malignant solid tumour of nerve tissue. It is most frequently located in the adrenal glands, but may occur in any part of the body, such as the neck, thorax, or spinal cord. It occurs most frequently before five years of age; on average at two years of age. Neuroblastoma is highly malignant. It has usually already spread by the time it is diagnosed. Tumours can grow in any part of the nervous system. Symptoms depend on the mass effect of the tumour in the affected region, which can be the head, neck, thorax, or paraspinal or lumbar sacral region. Neuroblastoma most frequently metastasises to the following sites: bones, lymph nodes, bone marrow, liver, and skin.

Bone and soft tissue tumours in children

Osteosarcoma is the most common bone tumour in children and adolescents with an annual incidence of approximately 5.1 cases per million in individuals younger than 20 years**.** The majority of osteosarcomas occur in the extremities. Ewing sarcoma is the second most common bone tumour in children and adolescents and can also present as a soft tissue malignancy.

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in children. In patients with localised disease, overall 5-year survival rates have improved to more than 80% with the combined

use of surgery, radiation therapy, and chemotherapy. However, in patients with metastatic disease, little progress has been made in survival rates, with a 5-year, event-free survival rate of less than 30%.

PICO 4: OTHER PICO - RELEVANT TUMOURS

This category consists of two types of cancer: Nephroblastoma and Adenoid cystic carcinoma of the lacrimal or salivary glands.

Nephroblastoma (also known as Wilms tumour) is the most common paediatric malignant neoplasm of the kidney cells, which compromises one or both kidneys. The condition occurs more with greatest frequency among 2 and 3 year-olds. It may be associated with congenital malformations and symptoms may include; haematuria, hypertension and pain.

Adenoid cystic carcinoma is a rare, slow growing tumour which originates in the epithelial tissue of the minor and major salivary glands and lacrimal glands.[14]

A.5.   COMPARATOR DETAILS

PASC advised that the population funded by the MTO Program is not a relevant population for comparison because it relates to the financial cost of a small group of patients travelling to receive treatment. It is noted that patients will no longer be eligible for MTO Program financial assistance once PBT facilities are operational in Australia. A decrease in incurred costs in relation to overseas treatment, travel and accommodation is considered in the financial modelling.

Potential comparators include conventional PRT. While PBT treatment planning and delivery have evolved, so too have other approaches to radiotherapy utilising photons. IMRT is a form of EBRT delivered with a linear accelerator ("linac"), that is defined by its ability to modulate beam intensity through the use of multi-leaf-collimators. In April 2015, MSAC supported public funding of IMRT for cancer treatment delivery on a cost minimisation basis as compared to three dimensional conformal radiotherapy (3D-CRT). The Public Summary Document noted that the intensity of the beams generated by IMRT is able to be modulated, resulting in a customisable radiation dose to target a tumour better, while sparing surrounding non-tumour tissues. IMRT is the most relevant comparative radiation therapy treatment funded on the MBS, (Advice from contracted assessment clinical experts in August 2017).

The MBS item descriptors for IMRT are summarised in Table 8.

Table 8   Relevant MBS item for IMRT

MBS Item Number	MBS Description	Scheduled Fee
15275	RADIATION ONCOLOGY TREATMENT with IGRT imaging facilities undertaken: (a) To implement an IMRT dosimetry plan prepared in accordance with item 15565; and (b) utilising an intensity modulated treatment delivery mode (delivered by a fixed or dynamic gantry linear accelerator or by a helical non C-arm based linear accelerator), once only at each attendance at which treatment is given.	$182.90
15565	Preparation of an IMRT DOSIMETRY PLAN, which uses one or more CT image volume datasets, if: (a) in preparing the IMRT dosimetry plan: (i) the differential between target dose and normal tissue dose is maximised, based on a review and assessment by a radiation oncologist; and (ii) all gross tumour targets, clinical targets, planning targets and organs at risk are rendered as volumes as defined in the prescription; and (iii) organs at risk are nominated as planning dose goals or constraints and the prescription specifies the organs at risk as dose goals or constraints; and (iv) dose calculations and dose volume histograms are generated in an inverse planned process, using a specialised calculation algorithm, with prescription and plan details approved and recorded in the plan; and (v) a CT image volume dataset is used for the relevant region to be planned and treated; and (vi) the CT images are suitable for the generation of quality digitally reconstructed radiographic images; and (b) the final IMRT dosimetry plan is validated by the radiation therapist and the medical physicist, using robust quality assurance processes that include: (i) determination of the accuracy of the dose fluence delivered by the multi-leaf collimator and gantry position (static or dynamic); and (ii) ensuring that the plan is deliverable, data transfer is acceptable and validation checks are completed on a linear accelerator; and (iii) validating the accuracy of the derived IMRT dosimetry plan in a known dosimetric phantom; (iv) determining the accuracy of planned doses in comparison to delivered doses to designated points within the phantom or dosimetry device; and (c) The final IMRT dosimetry plan is approved by the radiation oncologist prior to delivery.	$3,313.85
15715	RADIATION ONCOLOGY TREATMENT VERIFICATION of planar or volumetric IGRT for IMRT, involving the use of at least 2 planar image views or projections or 1 volumetric image set to facilitate a 3-dimensional adjustment to radiation treatment field positioning, if: (a) the treatment technique is classified as IMRT; and (b) the margins applied to volumes (clinical target volume or planning target volume) are tailored or reduced to minimise treatment related exposure of healthy or normal tissues; and (c) the decisions made using acquired images are based on action algorithms and are given effect immediately prior to or during treatment delivery by qualified and trained staff considering complex competing factors and using software driven modelling programs; and (d) the radiation treatment field positioning requires accuracy levels of less than 5 mm (curative cases) or up to 10 mm (palliative cases) to ensure accurate dose delivery to the target; and (e) the image decisions and actions are documented in the patient's record; and (f) the radiation oncologist is responsible for supervising the process, including specifying the type and frequency of imaging, tolerance and action levels to be incorporated in the process, reviewing the trend analysis and any reports and relevant images during the treatment course and specifying action protocols as required; and (g) when treatment adjustments are inadequate to satisfy treatment protocol requirements, replanning is required; and (h) the imaging infrastructure (hardware and software) is linked to the treatment unit and networked to an image database, enabling both on line and off line reviews.	$76.60

Source: MBS Online accessed September 2017.
Abbreviations: MBS, Medicare Benefits Schedule; IMRT, intensity modulated radiation therapy; IGRT, image guided radiation therapy; CT, computed tomography.

Alternate radiotherapy modalities including: SBRT, other EBRT and brachytherapy may also be relevant based on the location to key organs. The PASC advised the preferred approach of clinicians is to compare and contrast a 'best practice photon plan' with a 'best practice proton plan', including calculating the maximum total dose to the tumour or minimum dose that could be achieved to critical

surrounding structures. These plans are then peer-reviewed by a panel to determine the best approach on an individual patient basis. Other treatment options specific to the clinical condition (e.g. surgery, chemotherapy, immunotherapy, other devices such as laser therapy for ocular tumours) are relevant comparators. Surgical resection may be conducted prior or post PBT therapy depending on the location and size of the tumour. Similarly, chemotherapy may be initiated as neo adjuvant or post adjuvant treatment with varied regimens depending on the aggressiveness of the neoplasm and patients ECOG performance status. PASC queried whether the comparator needs to be tumour specific. Clinicians at the meeting indicated that this is the practice in Denmark and the UK.

Best supportive care is also a relevant comparator for patients that have accessed the MTO Program because of the assessment that no alternative curative treatment can be administered due to risk of unacceptable toxicities secondary malignancy and proximity to organ structures. The preferred comparator was not clearly indicated by the PASC.

A.6. CLINICAL MANAGEMENT ALGORITHM(S)

PBT is of particular interest in treating tumours deriving from cranial spinal and ocular locations where conventional PRT would damage 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 the need to reduce overall radiation toxicity and secondary tumours is critical. Additionally, should the medical team subscribe to the ALARA principle, the proposed benefit of PBT should increase [15]. 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.

Accurate diagnosis and determination of prognostic factors for rare cancers require extensive pathology tests, biopsies and imaging techniques. The importance of the multidisciplinary team in initial assessment, diagnosis and making decisions about treatment is strongly endorsed by clinical guidelines. A multidisciplinary approach is preferred, involving pathologists, radiologists, surgeons, radiation therapists, medical oncologists and paediatric oncologists, with experience in the tumour type, and within reference networks sharing expertise and treating a high number of patients annually. This centralised referral should be pursued as early as at the time of the clinical diagnosis. The importance of appropriate diagnosis, including biopsy, review by an experienced histopathologic, and determination of grade and subtype to preoperative planning –particularly preoperative radiotherapy is highlighted in clinical guidelines.

CURRENT MANAGEMENT ALGORITHM

Based on the current clinical management algorithm, patients may receive financial assistance to travel overseas via MTO Program. To qualify for MTO Program the applicant must be an Australian citizen or be an Australian resident eligible to receive Medicare Benefits. The application assessment

process takes a minimum of six weeks. The patient must be suffering from a life threatening condition and meet the following four mandatory medical conditions:

1. The proposed overseas treatment or an effective alternative treatment must not be available in time to benefit the applicant.

2. The treatment must be significantly life extending and potentially curative.

3. There must be a realistic prospect of a cure and significant extension of life expectancy from the proposed treatment.

4. The treatment must be accepted by the Australian medical profession as a standard form of treatment for the applicants' condition.

Eligible patents must be supported by their treating Australian specialist and the Faculty of Radiation Oncology. A comparative proton versus photon plan is required to demonstrate the patient meets the clinical criteria to access MTO Program. The Australian Bragg Centre for Proton Therapy and Research (SAHMRI) are currently the only suppliers of proton/photon treatment comparisons plans used to support the MTO Program application process. All relevant clinical evidence are assessed by a panel of Departmental Medical Advisers. The overseas treatment location for PBT is nominated by the treating Australian specialist and historically most patients have travelled to the United States.

The current clinical algorithm in Figure 3 is a generalised representation of PBT with curative intent. In practice, treatment of the cancers of interest may be multi-modal (e.g. radiation therapy may be used in combination with surgery).

Figure 3   Current clinical management algorithm for PBT with curative intent (generalised representation)
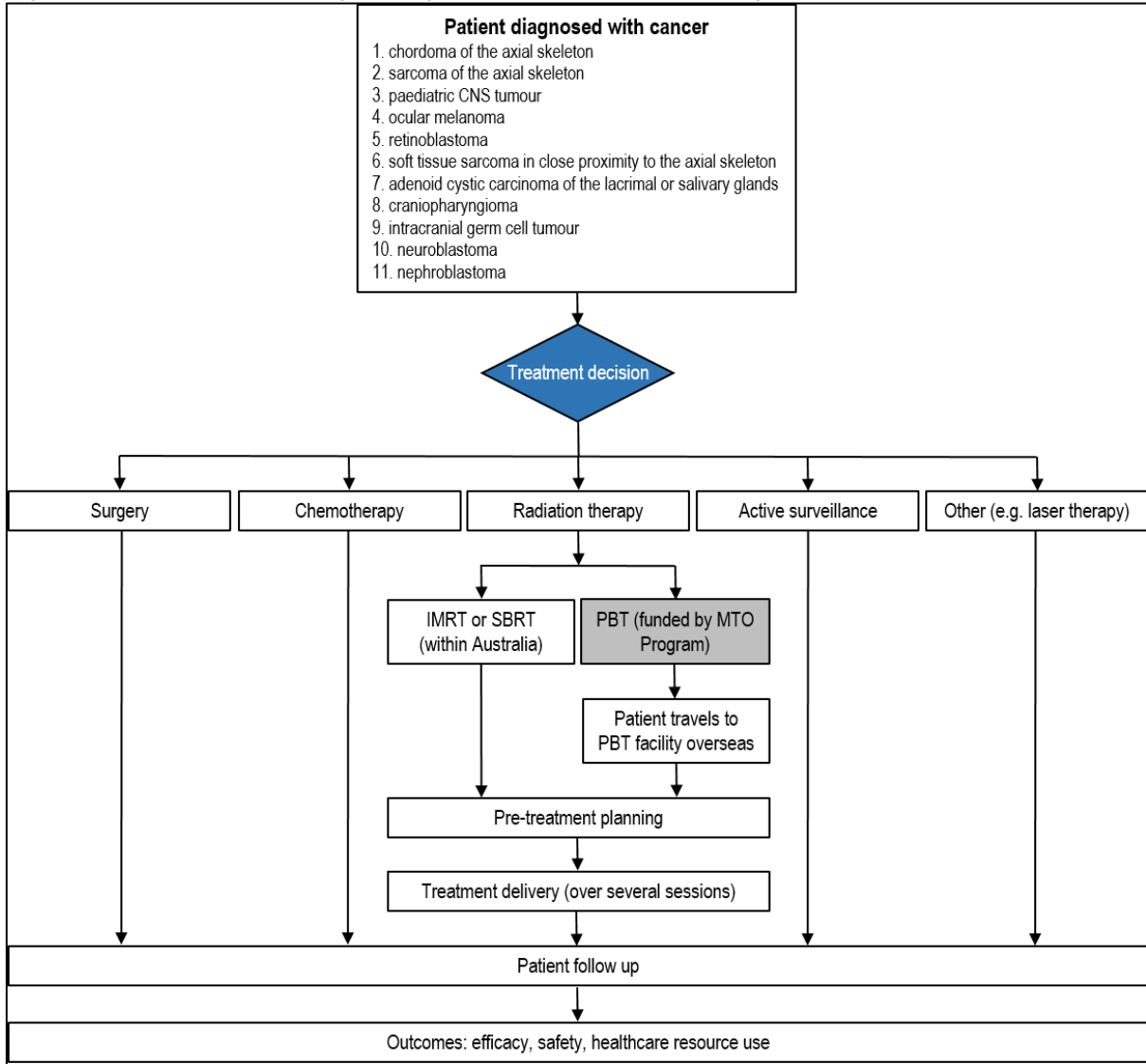
Source: Application 1455: Proton Beam Therapy (PBT). PICO Confirmation
Abbreviations: PBT, proton beam therapy; CNS, Central Nervous System; IMRT, intensity modulated radiation therapy; SBRT, Stereotactic Body Radiation Therapy; MTO, Medical Treatment Overseas Program.

PROPOSED MANAGEMENT ALGORITHM

The proposed clinical management algorithm (Figure 4) assumes that PBT will be included on the MBS 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 (Refer to Section F for further details).

Figure 4   Proposed clinical management algorithm for PBT with curative intent (generalised representation)
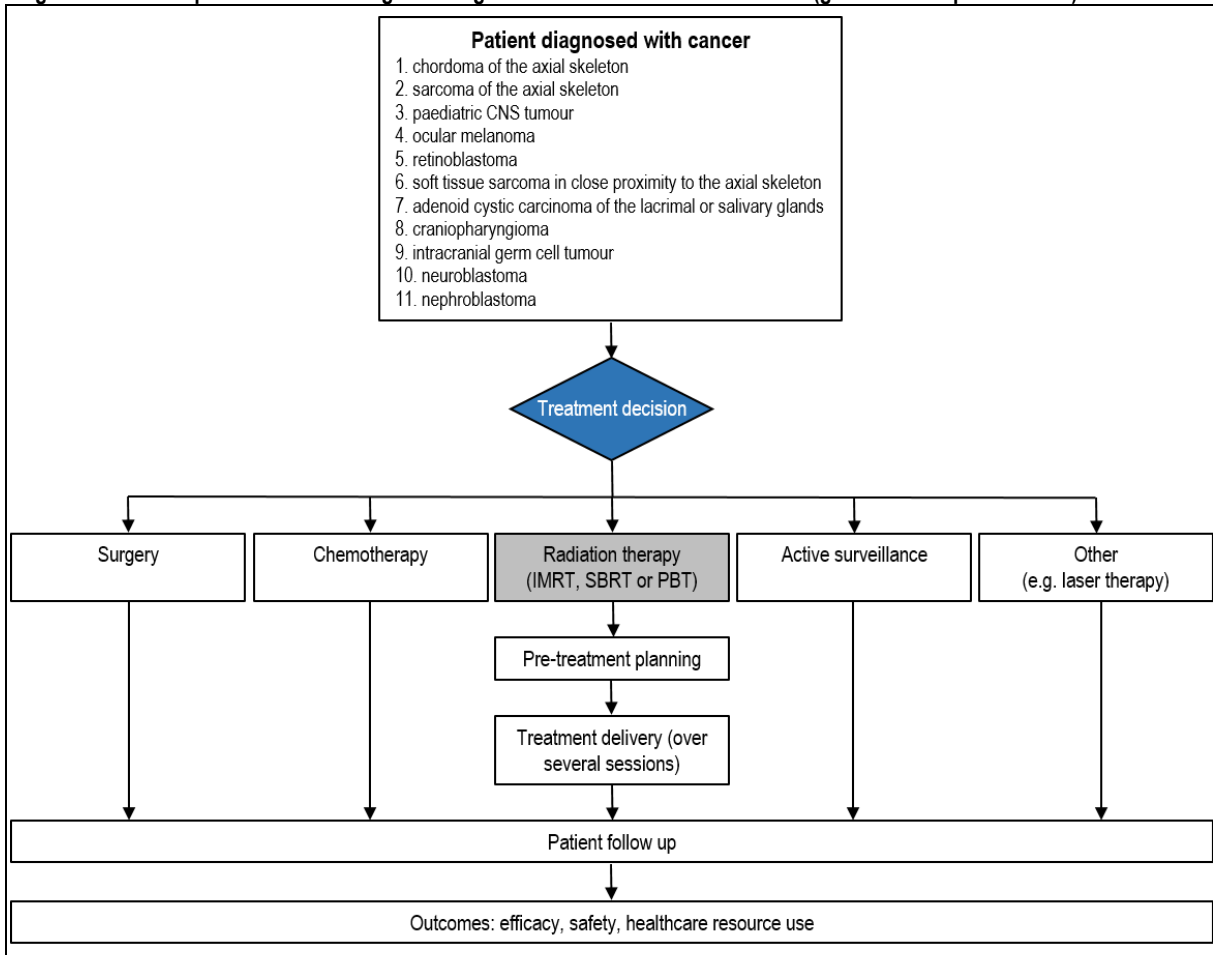
Source: Application 1455: Proton Beam Therapy (PBT). PICO Confirmation
Abbreviations: PBT, proton beam therapy; IMRT, intensity modulated radiation therapy; SBRT, Stereotactic Body Radiation Therapy.

A.7.   KEY DIFFERENCES IN THE DELIVERY OF THE PROPOSED MEDICAL SERVICE AND THE MAIN COMPARATOR

Section A.2 has outlined key differences in proton therapeutic technology compared to photon including underlying principles and delivery methods.

During our systematic literature review, the vast majority of past and current clinical studies compared PBT and PRT patients exposed to the same number of fractions. Therefore, this Assessment Report will compare PBT with conventional treatment using the same number of treatment fractions.

The current clinical algorithm for the MTO Program requires comparative proton and photon therapy plans. This section outlines key differences required for proton planning.

Both PBT and PRT treatment planning is complex. Dose distributions for each of the beams are computed by the treatment planning system (TPS) and summed, with appropriate weighting, to produce the composite optimum dose distribution expected to be delivered. In the current state-of-the-art, semi-empirical analytical formalisms and algorithms are used for such computations.

Common standard treatment planning systems available include; Eclipse, Pinnacle3, RayStation and XiO.

The approximations and assumptions of these methods and of the software systems based on them, contribute to the overall uncertainty in dose distributions delivered. Protons have a finite range, positioning of the dose gradients is therefore critical to successful planning and treatment. An uncertainty of even a few millimetres can lead to under dosage in the target volume or over dosage of an OAR. The variables that give rise to uncertainties in the range prediction can be divided into two main groups: those causing uncertainties in the range calculation in the TPS and those leading to discrepancies between planning dose and delivered dose[16]. IMPT is more sensitive to dose range uncertainties and movement.

Range calculation uncertainties can arise from inaccurate data exported to the TPS. CT is used to acquire patient image data and the Hounsfield units (HUs) are then converted into proton stopping powers so dose calculations can be made. Errors arise in proton range calculation from CT-based plans owing to inaccuracy in the HU to proton stopping power conversion and inaccuracies in the HU values themselves. Inaccuracies in the HU values are caused by noise, CT artefacts and beam hardening. Research is being undertaken to develop proton CT technology has not yet resulted in images being available in the clinical setting[17].

Uncertainties are normally compensated for in PRT by introducing safety margins to produce a planning target volume (PTV) and planning OAR volume (PRV). A similar method has been recommended by the International Committee on Radiation Units and Measurements (ICRU) for PBT. The larger the safety margin, the less conformal the resulting dose distribution. To achieve an optimum proton treatment plan, the inclusion of uncertainties in the optimisation algorithm and a multi-objective Pareto optimisation function have been considered internationally[17].

The TPS calculations may be based on assumptions derived from limited patient information and may only include information from one treatment centre. To ensure the calculations are relevant for the Australian setting, coordination of Australian PBT patient case history for relevant cancer types and patient pathogenesis is critical for inclusion in the TPS. Web based systems such as ReCompare incorporate information from conventional PRT planning, individual treatment centres and source data from a central database to generate a comparative proton/photon plan for individual patients. The robustness of the TPS should also be assessed with comparison across different systems, as part of the verification process

A.8.   CLINICAL CLAIM

The clinical claim from the PICO is that PBT is superior in clinical effectiveness and either non-inferior or superior in safety to usual standard of care. The indicated economic analysis is, therefore a cost-utility or a cost-effectiveness analysis.

Even though the PICO claim was superior clinical effectiveness and either non-inferior or superior in safety, the review of the evidence did not reveal these results. There is not sufficient quality evidence to support this claim. The evidence reviewed documented substantial uncertainty as regards to this claim.

Therefore, the resulting economic evaluation was a cost consequences approach, since comparative effectiveness could not be substantiated.

A.9. SUMMARY OF THE PICO

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

The PICO that were pre-specified to guide the systematic literature review are presented in Box 1 to Box 8. This is the rationale behind the categorisation:

1) Based on the pre-defined inclusions and exclusion criteria for our evidence base and direct reflection of the indications defined in the PICO document
2) Anatomical position of tumours
3) Clinical definition of tumour classes. e.g. neuroblastomas are defined as peripheral neuroblastic tumours that occur outside of the CNS and therefore were not categorised as brain tumours
4) Incidence rate of specific tumours in the adult versus paediatric population. e.g. neuroblastoma, retinoblastoma, nephroblastoma
5) It should be noted that some tumours could fit under more than one category e.g. retinoblastoma for "Paediatric" and "Ocular" categories; nephroblastoma/Wilms tumour for "Paediatric" and "Other" categories

PICO 1: HEAD/SKELETON TUMOURS

PBT is a highly conformal form of radiation treatment that potentially better targets cancerous tissue with less irradiation of adjacent healthy tissue. PBT therefore offer advantages to the treatment of head and skeleton tumours that are traditionally difficult to treat.

Box 1 Criteria for identifying and selecting studies to determine the safety of adults PBT in patients with head and skeleton tumours

Selection criteria	Description
Population	Chordoma of the axial skeleton (defined as the skull, vertebral column and bony pelvis). Sarcoma of the axial skeleton (including chondrosarcoma). Intracranial germ cell tumour. Soft tissue sarcoma in close proximity to the axial skeleton (to include rhabdomyosarcoma). Craniopharyngioma.
Intervention	PBT with curative intent (primary treatment of the condition) or as salvage treatment (for recurrent disease or after failure of initial therapy); as monotherapy; as a 'boost' mechanism to conventional PRT; or in combination with other modalities, such as chemotherapy and/or surgery.
Comparator	The preferred comparator was not clearly resolved by the PASC. Conventional clinical comparators include radiation therapy alternatives, such as IMRT, SBRT or other EBRT, and also brachytherapy. Other modalities such as chemotherapy and/or surgical resection were also considered as comparators.
Outcomes	Critical for decision making: Acute radiation-related toxicities (i.e. within the first 90 days after treatment), Late radiation-related toxicities (i.e. >90 days after treatment) Radiation dose Important, but not critical for decision making: None Low importance for decision making: Systemic effects such as fatigue, erythema or hair loss
Systematic review question	Is PBT comparatively safer than alternative treatments for head and skeleton tumours in adults?

Abbreviations: PBT, proton beam therapy; PRT, photon radiation therapy; PASC, PICO Advisory Sub-Committee; IMRT, intensity modulated radiation therapy; SBRT, stereotactic body radiation therapy.

Box 2   Criteria for identifying and selecting studies to determine the effectiveness of PBT in adult patients with head and skeleton tumours

Selection criteria	Description
Population	Chordoma of the axial skeleton (defined as the skull, vertebral column and bony pelvis). Sarcoma of the axial skeleton. Intracranial germ cell tumour. Soft tissue sarcoma in close proximity to the axial skeleton (to include rhabdomyosarcoma). Craniopharyngioma.
Intervention	PBT with curative intent (primary treatment of the condition) or as salvage treatment (for recurrent disease or after failure of initial therapy); as monotherapy; as a 'boost' mechanism to conventional PRT; or in combination with other modalities, such as chemotherapy and/or surgery.
Comparator	The preferred comparator was not clearly resolved by the PASC. Conventional clinical comparators include radiation therapy alternatives, such as IMRT, SBRT or other EBRT, and also brachytherapy. Other modalities such as chemotherapy and/or surgical resection were also considered as comparators.
Outcomes	Critical for decision making: - Disease-free and/or overall survival - Disease-related and/or - All-cause mortality - Disease progression - Local tumour control - Regression/remission) - Incidence of metastases - Health-related quality of life (HRQoL) Important, but not critical for decision making: None Low importance for decision making: None
Systematic review question	Does PBT improve patient efficacy compared to alternative treatments for head and skeleton tumours in adults?

Abbreviations: HRQoL, Health-related quality of life; PBT, proton beam therapy; PRT, photon radiation therapy; PASC, PICO Advisory Sub-Committee; IMRT, intensity modulated radiation therapy; SBRT, stereotactic body radiation therapy.

PICO 2: OCULAR TUMOURS

PBT is a highly conformal form of radiation treatment that potentially better targets cancerous tissue with less irradiation of other normal tissue, compared to conventional PRT. PBT therefore may be benefit to patients with ocular tumours.

Box 3   Criteria for identifying and selecting studies to determine the safety of PBT in adults with ocular melanoma

Selection criteria	Description
Population	Ocular melanoma
Intervention	PBT with curative intent (primary treatment of the condition) or as salvage treatment (for recurrent disease or after failure of initial therapy); as monotherapy; as a 'boost' mechanism to conventional PRT; or in combination with other modalities, such as chemotherapy and/or surgery.
Comparator	The preferred comparator was not clearly resolved by the PASC. Conventional clinical comparators include radiation therapy alternatives, such as IMRT, SBRT or other EBRT, and also brachytherapy. Other modalities such as chemotherapy and/or surgical resection were also considered as comparators.
Outcomes	Critical for decision making: Acute radiation-related toxicities (i.e. within the first 90 days after treatment), Late radiation-related toxicities (i.e. >90 days after treatment) Secondary malignancy Radiation dose Important, but not critical for decision making: Enucleation rates Low importance for decision making: Systemic effects such as fatigue, erythema or hair loss
Systematic review question	Is PBT comparatively safer than alternative treatments for adult patients with ocular melanoma?

Abbreviations: PBT, proton beam therapy; PRT, photon radiation therapy; PASC, PICO Advisory Sub-Committee; IMRT, intensity modulated radiation therapy; SBRT, stereotactic body radiation therapy.

Box 4   Criteria for identifying and selecting studies to determine the efficacy of PBT in adult patients with ocular melanoma

Selection criteria	Description
Population	Ocular melanoma
Intervention	PBT with curative intent (primary treatment of the condition) or as salvage treatment (for recurrent disease or after failure of initial therapy); as monotherapy; as a 'boost' mechanism to conventional PRT; or in combination with other modalities, such as chemotherapy and/or surgery.
Comparator	The preferred comparator was not clearly resolved by the PASC. Conventional clinical comparators include radiation therapy alternatives, such as IMRT, SBRT or other EBRT, and also brachytherapy. Other modalities such as chemotherapy and/or surgical resection were also considered as comparators.
Outcomes	Critical for decision making: Disease-free and/or overall survival Disease-related and/or all-cause mortality Disease progression Local tumour control regression/remission Incidence of metastases Visual acuity Health-related quality of life Important, but not critical for decision making: None Low importance for decision making: None
Systematic review question	Does PBT improve patient efficacy compared to alternative treatments for adult patients with ocular melanoma?

Abbreviations: PBT, proton beam therapy; PRT, photon radiation therapy; PASC, PICO Advisory Sub-Committee; IMRT, intensity modulated radiation therapy; SBRT, stereotactic body radiation therapy.

PICO 3: PAEDIATRIC AND ADOLESCENT TUMOURS OUTLINED IN THE PICO

PBT is a highly conformal form of radiation treatment that potentially better targets cancerous tissue with less irradiation of other normal tissue. PBT therefore may be benefit to paediatric and adolescent patients with tumours.

Box 5   Criteria for identifying and selecting studies to determine the safety of PBT in paediatric and adolescent patients

Selection criteria	Description
Population	Paediatric CNS tumour (including craniopharyngioma, intracranial germ cell tumour, meningioma, gliomas, ependymoma, medulloblastoma) Retinoblastoma Neuroblastoma
Intervention	PBT with curative intent (primary treatment of the condition) or as salvage treatment (for recurrent disease or after failure of initial therapy); as monotherapy; as a 'boost' mechanism to conventional PRT; or in combination with other modalities, such as chemotherapy and/or surgery.
Comparator	The preferred comparator was not clearly resolved by the PASC. Conventional clinical comparators include radiation therapy alternatives, such as IMRT, SBRT or other EBRT, and also brachytherapy. Other modalities such as chemotherapy and/or surgical resection were also considered as comparators.
Outcomes	Critical for decision making: Acute radiation-related toxicities (i.e. within the first 90 days after treatment), Late radiation-related toxicities (i.e. >90 days after treatment) Secondary malignancy Radiation dose Enucleation rates Neurocognitive impairment or cardiac toxicity. Important, but not critical for decision making: None Low importance for decision making: Systemic effects such as fatigue, erythema or hair loss
Systematic review question	Is PBT comparatively safer than alternative treatments for paediatric patients and adolescent with tumours outlined in the PICO population?

Abbreviations: PBT, proton beam therapy; PRT, photon radiation therapy; PASC, PICO, Population Intervention, Comparator, Outcome; PICO Advisory Sub-Committee; IMRT, intensity modulated radiation therapy; SBRT, stereotactic body radiation therapy.

Box 6   Criteria for identifying and selecting studies to determine the efficacy of PBT in paediatric and adolescent patients

Selection criteria	Description
Population	Paediatric CNS tumour (including craniopharyngioma, intracranial germ cell tumour, meningioma, gliomas, ependymoma, medulloblastoma) Neuroblastoma Retinoblastoma
Intervention	PBT with curative intent (primary treatment of the condition) or as salvage treatment (for recurrent disease or after failure of initial therapy); as monotherapy; as a 'boost' mechanism to conventional PRT; or in combination with other modalities, such as chemotherapy and/or surgery.
Comparator	The preferred comparator was not clearly resolved by the PASC. Conventional clinical comparators include radiation therapy alternatives, such as IMRT, SBRT or other EBRT, and also brachytherapy. Other modalities such as chemotherapy and/or surgical resection were also considered as comparators.
Outcomes	Critical for decision making: Disease-free and/or overall survival Disease-related and/or all-cause mortality Disease progression Local tumour control Regression/remission) Incidence of metastases Visual acuity & deafness Health-related quality of life Important, but not critical for decision making: None Low importance for decision making: None
Systematic review question	Does PBT improve patient efficacy compared to alternative treatments for paediatric and adolescent patients with tumours outlined in the PICO population?

Abbreviations: CNS, Central Nervous System; PBT, proton beam therapy; PRT, photon radiation therapy; PASC, PICO, Population Intervention, Comparator, Outcome; PICO Advisory Sub-Committee; IMRT, intensity modulated radiation therapy; SBRT, stereotactic body radiation therapy.

PICO 4: OTHER PICO-RELEVANT TUMOURS

PBT is a highly conformal form of radiation treatment that potentially better targets cancerous tissue with less irradiation of other normal tissue, compared to conventional PRT. PBT therefore may be of benefit to patients with other tumours defined in the PICO Confirmation, not listed in PICO 1 – 3.

Box 7   Criteria for identifying and selecting studies to determine the safety of PBT in adults with adenoid cystic carcinoma of the lacrimal or salivary glands or nephroblastoma

Selection criteria	Description
Population	Adenoid cystic carcinoma of the lacrimal or salivary glands Nephroblastoma
Intervention	PBT with curative intent (primary treatment of the condition) or as salvage treatment (for recurrent disease or after failure of initial therapy); as monotherapy; as a 'boost' mechanism to conventional PRT; or in combination with other modalities, such as chemotherapy and/or surgery.
Comparator	The preferred comparator was not clearly resolved by the PASC. Conventional clinical comparators include radiation therapy alternatives, such as IMRT, SBRT or other EBRT, and also brachytherapy. Other modalities such as chemotherapy and/or surgical resection were also considered as comparators.
Outcomes	Critical for decision making: Acute radiation-related toxicities (i.e. within the first 90 days after treatment), Late radiation-related toxicities (i.e. >90 days after treatment) Secondary malignancy Radiation dose Important, but not critical for decision making: Enucleation rates Low importance for decision making: Systemic effects such as fatigue, erythema or hair loss
Systematic review question	Is PBT comparatively safer than alternative treatments for adult patients with Adenoid cystic carcinoma of the lacrimal or salivary glands or nephroblastoma?

Abbreviations: PBT, proton beam therapy; PRT, photon radiation therapy; PASC, PICO Advisory Sub-Committee; IMRT, intensity modulated radiation therapy; SBRT, stereotactic body radiation therapy.

Box 8   Criteria for identifying and selecting studies to determine the efficacy of PBT in adults with adenoid cystic carcinoma of the lacrimal or salivary glands or nephroblastoma

Selection criteria	Description
Population	Adenoid cystic carcinoma of the lacrimal or salivary glands Nephroblastoma
Intervention	PBT with curative intent (primary treatment of the condition) or as salvage treatment (for recurrent disease or after failure of initial therapy); as monotherapy; as a 'boost' mechanism to conventional PRT; or in combination with other modalities, such as chemotherapy and/or surgery.
Comparator	The preferred comparator was not clearly resolved by the PASC. Conventional clinical comparators include radiation therapy alternatives, such as IMRT, SBRT or other EBRT, and also brachytherapy. Other modalities such as chemotherapy and/or surgical resection were also considered as comparators.
Outcomes	Critical for decision making: Disease-free and/or overall survival Disease-related and/or all-cause mortality Disease progression Local tumour control regression/remission Incidence of metastases Visual acuity Health-related quality of life Important, but not critical for decision making: None Low importance for decision making: None
Systematic review question	Does proton therapy improve patient efficacy compared to alternative treatments for adult patients with adenoid cystic carcinoma of the lacrimal or salivary glands or nephroblastoma?

Abbreviations: PBT, proton beam therapy; PRT, photon radiation therapy; PASC, PICO Advisory Sub-Committee; IMRT, intensity modulated radiation therapy; SBRT, stereotactic body radiation therapy.

A.10.   CONSUMER IMPACT STATEMENT

A total of fourteen responses were received by the Department during the consumer consultation process. Stakeholders were asked specific questions following the public release of the draft PICO Confirmation on the MSAC Application 1455 – Proton Beam Therapy. A number of consumer and clinical representative organisations provided advice. The following summarises the consumer issues and policy impacts identified.

CONSUMER ISSUES WITH PROPOSED POPULATION

PBT is significant for difficult cancers of the head and neck, brain, eye and CNS, skull base where there is no comparable curative treatment. Stakeholders were concerned should a PBT facility be made available in Australia, there is a risk that patients currently eligible for financial assistance under MTO Program will no longer be eligible for reimbursement of their treatment costs as patients will not meet Criterion A of the mandatory MTO Program eligibility criteria. In addition, there is no current applicable MBS listing. Patients in some States and Territories may be in the situation of deciding on paying the entire cost of the PBT treatment by themselves, resulting in patient affordability issues and inequitable patient access to treatment.

If a PBT facility is established in Australia, 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

It is acknowledged that PBT is a highly conformal form of radiation treatment that could potentially target cancerous tissue more accurately than IMRT while also giving less irradiation to healthy tissue. It is however, only known to be useful for a limited range of malignancies. It is recognised that 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.

PROPOSED COMPARATOR

PBT treatment planning and delivery have advanced over time, but so too have other approaches to radiotherapy. In early 2015, the MSAC supported public funding of IMRT for cancer treatment delivery. The intensity of the beams generated by IMRT is able to be modulated, resulting in a customisable radiation distribution to target tumours better, while relatively sparing surrounding non-tumour tissues.

Evidence of the effectiveness PBT, either alone or in combination with other therapies, is difficult to access due to the limited number of randomised controlled trials (RCTs). To date, clinical data does

not clearly demonstrate the benefit of better targeting with PBT for most tumour types. Further, comparative studies have not been conducted for paediatric cancers despite uncertainty over long-term outcomes, or for rare cancers. In view of the limited data available from comparative studies on PBT, appropriate scientific and clinical research on PBT may be further required to inform decisions on introducing and financing PBT technology in Australia.

PROPOSED OUTCOME

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 secondary malignant tumours. A reduction in the radiation dose to surrounding normal tissues may also allow an adequate dose to be delivered to tumours in close proximity to critical structures, and dose escalation to improve disease control.

PROPOSED ECONOMIC ANALYSIS

PBT will require additional intervention such as operational planning of increased paediatrics, anaesthetics and post-treatment services i.e. occupational therapists and speech pathologists. Patient out-of-pocket expenses may arise should there be a need to travel to another city for treatment. Costs to the MBS are expected. However, at this stage, the amounts are not quantifiable. We can assume that this number will be high due to increasing consumer interest in PBT technology and a number of states considering establishing PBT facilities. Potential domestic demand for this treatment modality is difficult to estimate.

CLINICAL MANAGEMENT ALGORITHM

There is currently limited clinical expertise on PBT in Australia. There will be a requirement for formal particle therapy training and credentialing for radiation oncologists, medical physicists and radiation therapists. This will more than likely necessitate the engagement of international experts to provide local training or for Australian professionals to undergo training overseas.

SECTION B   CLINICAL EVALUATION

Is PBT Safer and More Effective Than Alternative Cancer Therapies?

B.1.   LITERATURE SOURCES AND SEARCH STRATEGIES

The systematic review questions outlined in Section A9 are aimed at identifying and contrasting the safety and clinical effectiveness of PBT against other cancer therapies in common practice. To address these research questions, a systematic literature review was conducted to identify relevant national and international publications reporting on the therapeutic use of PBT in the PICO population.

Previous PBT HTA reports were also sought. The 2014 Washington State Health Care Authority HTA by the Institute for Clinical and Economic Review (Inst.CER) was found to provide a high quality evaluation on the clinical application of PBT for specific cancer cases[7]. The Inst.CER HTA comprehensively covered studies published between January 1990 and February 2014. The current clinical evaluation builds on this knowledge base.

Clinical literature was searched periodically between July to September 2017 to identify relevant studies and systematic reviews published from 2014 onwards. Searches were conducted in the databases and sources described in Appendix B. Keywords used in the searches are listed in Table 9.

Table 9 Search terms used

Element of clinical question	Search terms
Population	cancers, neoplasms, tumours
Intervention	proton beam therapy; proton therapy
Comparator (if applicable)	not included in literature search
Outcomes (if applicable)	not included in literature search
Limits	not proton pump inhibitors

B.2.   RESULTS OF LITERATURE SEARCH

A PRISMA flowchart (Figure 5) provides a graphic depiction of the results of the literature search and the application of the study selection criteria. Studies were selected independently by two reviewers.

Figure 5   Summary of the process used to identify and select studies for the assessment
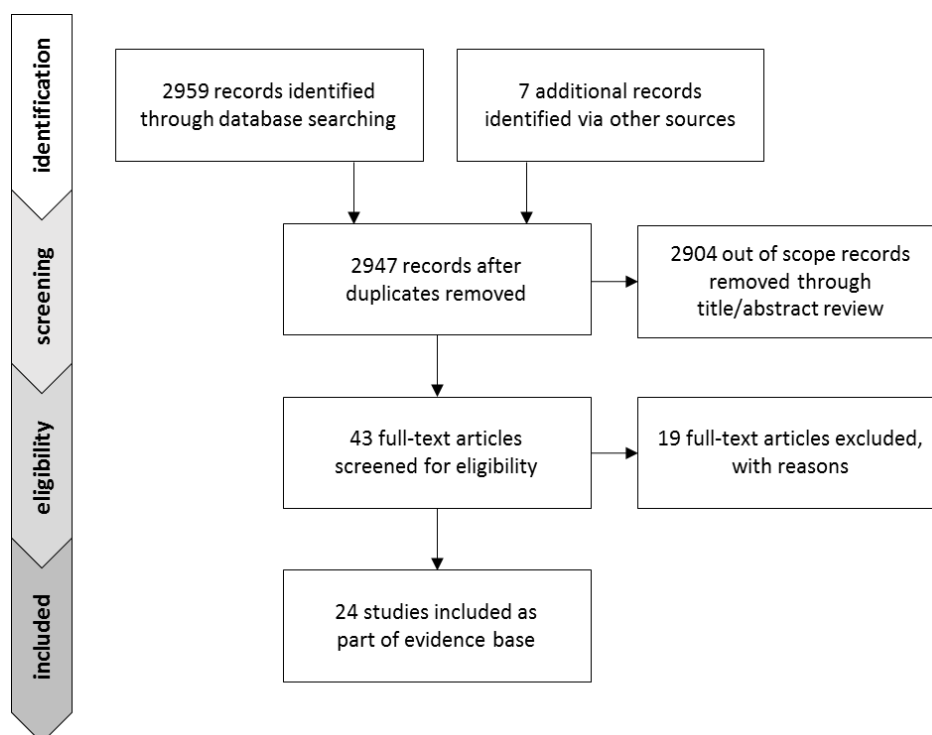
Following the identification and collection of medical publications, out of scope studies were excluded based on the following pre-specified criteria:

- Unsuitable publication type – individual case reports or level IV clinical case series, non-human and in vitro studies, incomplete studies or not peer-reviewed (e.g. editorials, letters, conference proceedings, abstracts without full-text).
- Published prior to 2014 – assessed as part of the Inst.CER HTA report; either included as part of evidence base or excluded.
- Description of methodology only – provides technical details of PBT techniques or other research protocols but no defined patient population in PBT planning, and no reporting on efficacy or other clinical outcomes.
- Non-English.
- Small sample size – less than five patients per study arm.
- Wrong population – not in the following populations:
  - PICO 1: Bone and soft tissue tumours
  - PICO 2: Ocular tumours
  - PICO 3: Paediatric cancers
  - PICO 4: Other PICO cancer populations, including patents with nephroblastoma and adenoid cystic carcinoma
- Wrong intervention – studies using PBT for purposes other than curative or salvage intent.
- Unsuitable outcomes – did not at least report on the clinical effectiveness of PBT.

Studies that could not be retrieved or that met the inclusion criteria but contained insufficient or inadequate data for inclusion are listed as Excluded Studies in Appendix D. All other studies that met the inclusion criteria are listed in Table 10 and Table 11.

A profile of each included study is given in Appendix C. This study profile describes the authors or study ID, publication year, study design and quality (level of evidence and risk of bias), study location, length of follow-up of patients, study population characteristics, description of the intervention, description of the comparator and the relevant outcomes assessed. Study characteristics are also summarised in a shorter format in Section B.4.

APPRAISAL OF THE EVIDENCE

Appraisal of the evidence was conducted in four stages:

- **Stage 1:** Appraisal of the risk of bias within individual studies or systematic reviews included in the review. Risk of bias items were assessed for the study as a whole. (Section B.3).

- **Stage 2:** Extraction of the pre-specified outcomes for this assessment, synthesising (meta-analysing or a narrative synthesis) to determine an estimate of effect per outcome.

- **Stage 3:** The quality of the evidence was graded using the NHMRC Evidence Hierarchy[18].

- **Stage 4:** Integration of this evidence for conclusions about the net clinical benefit of the intervention in the context of Australian clinical practice. (Sections B.6-8).

B.3. RISK OF BIAS ASSESSMENT

The risk of bias in systematic reviews was assessed using the ROBIS tool[19], a framework ideal for evaluating evidence from reviews of clinical interventions such as PBT. The ROBIS tool measures risk of bias across four key domains of a text: inclusion of a study eligibility criteria, extent of the identification and selection of studies, level of data collection and study appraisal, and the overall synthesis and findings of the review.

The Cochrane Collaboration tool[20] is useful for assessing risk of bias in RCTs, however, no relevant RCT reports were published from January 2014 to September 2017 as part of the scope and inclusion criteria for this clinical evaluation.

The ROBINS-I tool[21] was utilised to assess risk of bias for non-randomised comparative studies on the effectiveness of PBT against other oncology interventions. The ROBINS-I tool considers risk of bias across seven domains of a study: confounding factors that may influence outcomes of interest, selection process of study participants, the extent of differential or non-differential misclassification of intervention status, bias due to deviations from intended interventions, level of data completeness, potential for errors in measurement of outcome data, and the selection of reported results.

Overall risk of bias judgements for individual papers is shown in Table 10 and Table 11 and Appendix C.

B.4.   CHARACTERISTICS OF THE EVIDENCE BASE

See Appendix C for details on the individual studies included in the evidence base.

The quality of research papers included in this clinical evaluation was assessed using NHMRC's standard for clinical practice guidelines. Specifically, evidence was graded using the NHMRC Evidence Hierarchy[18]. A summary is provided in Table 10 and Table 11.

Five SRs and two HTAs were collected after the application of exclusion and inclusion criteria. No published results from completed RCTs were identified for the period between January 2014 and September 2017. However, six active RCTs currently in progress were found and are listed in Section F2. Seventeen non-randomised comparative effectiveness studies were collected. These papers provided details on the clinical effectiveness of PBT against other cancer therapies (comparators). Comparators of interest included primary therapies such as PRT, IMRT, surgical resection, chemotherapy, brachytherapy or carbon ion therapy (CIT). Comparators for clinical evaluation also included the use of PBT treatment plans in combination with any of these alternative modalities.

Results from the literature search did not address all the pre-defined PICO criteria. For instance, quality clinical data on the use of PBT in nephroblastoma patients were not identified. There were also no comparative cohort studies examining the safety and efficacy of PBT against a non-treated study arm of cancer patients, most likely due to ethical concerns.

Table 10   Key features of included Level I evidence

Study	Number of inclusions	Format	Risk of bias (ROBIS)	Relevant PICO populations	Key points
CADTH, 2017[22]	11	HTA	low risk of bias	chordomas and sarcomas of or near the axial skeleton, ocular melanomas, craniopharyngiomas, neuroblastomas, retinoblastomas, and paediatric CNS tumours	**Scope:** Includes a systematic literature search which was conducted in March 2017. Meta-analyses, previous systematic reviews and HTA reports, and grey literature from professional associations published between January 2007 and June 2017 primarily made up the inclusion criteria. **Author's Summary:** The safety and efficacy of PBT, alone or in combination with photon radiotherapy, compared with other types of radiotherapy, varied by the type of cancer. Interventional use of PBT on bone cancers, childhood craniopharyngiomas, medulloblastomas, and spinal gliomas offered no significant benefits in clinical outcomes. The efficacy of PBT on ocular malignancies appeared incoherent across multiple studies. Taken together 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.
Fossati P. et al., 2016[23]	15	systematic review	unclear risk of bias	chordoma, chondrosarcoma	**Scope:** Retrospective case series from 1999 that may include different tumour types. Studies containing paediatric patients and re-irradiation for relapse after photon radiotherapy were excluded. **Author's Summary**: Results in terms of local control and survival at 5 years appear more favourable for chondrosarcoma cohorts over those presenting with chordomas. Literature describes severe late side effects in a relatively small percentage of patients. For malignant tumours, such as chordoma and chondrosarcoma, proton radio therapy should be the first option over photon-based alternatives.
Inst.CER, 2014[7]	6 unique RCTs and 29 non-randomised comparative cohort studies	HTA	low risk of bias	chordomas and sarcomas of or near the axial skeleton, ocular melanomas, craniopharyngiomas, neuroblastomas, retinoblastomas, and paediatric CNS tumours	**Scope:** Systematically reviews studies from 1990 to 2014, including six RCTs as well as comparative cohort studies with a focus on the clinical effectiveness and harms PBT against one or more alternate treatment modalities. Brief summaries of case series studies reporting on PBT for cancer patients are also tabulated. **Author's Summary:** "…there are significant uncertainties that remain with the delivery of proton beams for a variety of tumour types and locations, including physical uncertainty at the end of the beam range and penumbra effects, as well as concerns regarding the effects of neutron radiation produced by PBT and a lack of precise understanding of PBT's relative biological effectiveness for all tumour types and tissue depths."
Laprie A. et al., 2015[24]	40 clinical studies and 60 publications reporting PBT clinical outcomes	systematic review	unclear risk of bias	paediatric CNS tumours, germinoma (germ cell tumour), craniopharyngioma	**Scope:** Papers on paediatric brain tumours between 1966 and 2014. A focus on efficacy of PBT on various cancer types according to overall survival, event-free survival and local tumour control. **Author's Summary:** Evidence-based recommendations are made for PBT use on childhood craniospinal gliomas and medulloblastomas, malignancies within completely grown spinal canals of adolescents, as well as ependymomas and germinomas in patients less than 12 years of age. PBT is linked to favourable clinical outcomes for these tumour classes in young patients. However, concerns are raised in the literature regarding PBT use for craniopharyngiomas, given the risks involved with toxicities affecting physical and neurocognitive development, and quality of life.

Study	Number of inclusions	Format	Risk of bias (ROBIS)	Relevant PICO populations	Key points
Leroy R. et al., 2016[25]	23	systematic review	low risk of bias	paediatric CNS tumours, craniopharyngioma, retinoblastoma, neuroblastoma	**Scope:** First systematic review of medical literature dedicated to PBT use on paediatric cancers. Majority of the included body of evidence consisted of case series with only two comparative cohort studies assessed. No randomised clinical trials were identified, likely due to the rare and heterogenous nature of childhood cancers. **Author's Summary:** While PBT undoubtedly reduces the radiation dose to normal tissues and organs, to date, coherent clinical evidence on the long-term effectiveness and harms associated with PT in numerous paediatric cancers requires further research. Clinical application of PBT still has to contend with some limitations and disadvantages, such as focus of the target field (e.g. magnitude of lateral penumbra, distal edge degradation), uncertainty regarding the relative biological effectiveness which may vary per tissue and dose applied.
Matloob S.A. et al., 2016[26]	12	systematic review	unclear risk of bias	skull base (clival) chordomas	**Scope:** Systematic review of indications and efficacy of PBT as adjuvant radiotherapy to surgical resection of skull base chordomas. A literature search and systematic appraisal of articles from 1974-2016 resulted the detection of twelve key studies, which formed the primary focus of the review. **Author's Summary:** There are significant limitations in the evidence base, such as heterogeneity of study variables, incomplete detailing of the extent of tumour resection, surgical follow-ups not necessarily specified, grouping of tumour masses unmatched in gross volume. High class evidence does not exist for unequivocal recommendation of PBT in the management of chordomas. Further studies should be conducted to gain a better understanding of the indications, shortcomings, and areas of improvement for PBT, particularly in contrast to other available treatment modalities.
Verma V. and Mehta M.P., 2016[27]	14	systematic review	unclear risk of bias	ocular (uveal) melanoma	**Scope:** Systematic review conducted from 2000 to 2015 looking at the oncological and ophthalmological outcomes of PBT use for uveal melanomas. **Author's Summary:** Overall strong favourable outcomes are associated with PBT for uveal melanomas, particularly its effective tumouricidal activity and improved disease-free survival rates. However, inclusion of relatively small tumour size in studies is linked to an inflation of statistics. Additionally, there are varied PBT doses reported across studies, with earlier studies using a higher PBT dose while more recent studies use lower doses, likely to offset harms. Notably high rates of toxicity (e.g. near 25% enucleation rate) and complications have also been observed (e.g. Up to 30% glaucoma occurrence rate and up to 60% patients form cataracts).

Abbreviations: PICO, patients intervention comparator outcomes; Inst.CER, Institute for Clinical and Economic Review; PBT, proton beam therapy; CNS, central nervous system.

Table 11   Key features of the included evidence comparing intervention with comparator

Study	N (PBT-treated cohort)	Study design / Duration	Risk of bias (Cochrane)	Patient population	Key outcomes(s)
Level II completed RCTs					
No trial results published during 2014-2017					
Level III comparative effectiveness studies					
PICO 1: Brain, spinal and soft tissue cancers					
Molina C.A. et al., 2014[28]	9	retrospective comparative effectiveness / 2000-2008	critical risk of bias	chordomas	overall survival
Mima M. et al., 2014[29]	7	retrospective comparative effectiveness / 2005-2011	critical risk of bias	chordoma (sacral)	local tumour control, overall survival, safety (radiation dose)
Rotondo R.L. et al., 2015[30]	58	retrospective comparative effectiveness / 1982-2011	critical risk of bias	chordoma (spinal)	local tumour control, overall survival, safety (RT-specific toxicities)
Indelicato D.J. et al., 2016[31]	28	retrospective comparative effectiveness / 2007-2013	critical risk of bias	chordomas and chondrosarcomas	local tumour control, safety (radiation dose)
PICO 2: Ocular cancers					
Schonfeld S. et al., 2014[32]	18	retrospective comparative effectiveness / 1998-2005	critical risk of bias	ocular (choroidal) melanoma	disease-related mortality, incidence of metastasis, local tumour control, patient-relevant outcomes (visual acuity), safety (secondary glaucoma, cataract formation)
Sikuade M. et al., 2015[33]	106	retrospective comparative effectiveness / 2001-2011	critical risk of bias	ocular (choroidal) melanoma	overall survival, patient-relevant outcomes (visual acuity), safety (RT-related toxicity, radiation dose)
Seibel I. et al., 2017[34]	216	retrospective comparative effectiveness / 1998-2015	critical risk of bias	ocular (choroidal or ciliary body) melanoma	enucleation-free survival, safety (RT-related toxicity)
PICO 3: Paediatric and adolescent cancers					
Sethi R. et al., 2014[35]	55	retrospective comparative effectiveness / 1986-2011	critical risk of bias	retinoblastoma	incidence of distant metastasis, safety (rate of in-field RT-related secondary malignancies)

Study	N (PBT-treated cohort)	Study design / Duration	Risk of bias (Cochrane)	Patient population	Key outcomes(s)
Bishop A.J. et al., 2014[36]	21	retrospective comparative effectiveness / 1996-2012	critical risk of bias	craniopharyngioma	overall survival, safety (RT-related toxicities)
Yock T.I. et al., 2014[37]	57	retrospective comparative effectiveness / 1998-2007	critical risk of bias	paediatric CNS tumours	HRQoL
Song S. et al., 2014[38]	30	prospective comparative effectiveness / 2008-2012	critical risk of bias	paediatric CNS tumours	patient-relevant outcomes (freedom from blood product transfusion), safety (acute radiation-related toxicities)
Gunther J.R et al., 2015[39]	37	retrospective comparative effectiveness / 2000-2013	critical risk of bias	intracranial ependymoma	overall survival, recurrence rate, safety (acute and late RT-related toxicities)
Eaton B.R. et al., 2016[40]	45	prospective comparative effectiveness / 2000-2009	critical risk of bias	medulloblastoma	overall survival, local tumour control, safety (radiation dose)
Eaton B.R. et al., 2016[41]	40	retrospective comparative effectiveness / 2000-2009	critical risk of bias	medulloblastoma	patient-relevant outcomes (changes in height and BMI), safety (radiation dose, systemic effects eg. endocrinopathy)
Sato M. et al., 2017[42]	41	retrospective comparative effectiveness / 2000-2013	critical risk of bias	ependymoma	overall survival, disease progression, local recurrence rate, safety (RT-related toxicities)
PICO 4: Other PICO-relevant cancers					
Takagi M. et al., 2014[43]	6	retrospective comparative effectiveness / 2002-2012	critical risk of bias	salivary gland adenoid cystic carcinoma	local tumour control, overall survival, disease progression, safety (acute and late RT-related toxicities)
Romesser P.B. et al., 2016[44]	18	retrospective comparative effectiveness / 2011-2014	critical risk of bias	salivary gland carcinoma	local tumour control, overall survival, incidence of metastases, safety (acute RT-related toxicities, radiation dose)

Abbreviations: BMI, body mass index; CNS, central nervous system; Abbreviations: PICO, patients intervention comparator outcomes; PBT, proton beam therapy; RT, radiotherapy

B.5.   OUTCOME MEASURES AND ANALYSIS

An overview of SRs, RCTs, and non-randomised clinical studies of the comparative clinical effectiveness and safety of PBT to treat specific types of cancers was conducted. As part of the inclusion criteria for this clinical evaluation, studies must have had detailed at least one measure of clinical effectiveness for PBT compared to other standards of care for relevant PICO populations. Effectiveness of PBT intervention was measured in a clinical setting as rates of overall survival or disease-related mortality, disease progression, local tumour control or recurrence, freedom from metastasis, HRQoL, and/or other patient-relevant outcomes such as retained visual acuity for studies of ocular malignancies (Table 13).

In addition to tumoricidal effectiveness, other outcome measures regarding the safety of PBT were of interest (Table 12). Acute and late radiation-related toxicities, toxicities specific to a cancer type, radiation dose, and systemic side effects as a result of radiotherapy were examined as safety measures. Radiation exposure during treatment involves a high risk for mutagenic oncogenesis, causing radiation-induced secondary malignancies, which were also considered a safety outcome measure in this Assessment Report.

See Appendix C for details on the outcomes investigated in each included study, along with the range of statistical analyses used in each study. Conventional epidemiological measures of association were calculated from the results of individual publications, for instance, risk difference, number needed to harm/treat, and relative risk (Table 12 and Table 13). These afforded a method of normalisation and comparative analysis of patient related outcomes across multiple independent studies.

The evidence base incorporated in this Assessment Report is largely based on systematic reviews and non-randomised studies of retrospective comparative effectiveness; no prospective RCT publications were identified. Therefore, almost all reported clinical outcomes were derived from analytical and statistical methodologies designed post hoc. Indeed, there are limitations, and an elevated risk of bias in this setting, particular with the allocation of comparable cohorts and the potential for missing data.

B.6.   RESULTS OF THE SYSTEMATIC LITERATURE REVIEW

IS PBT SAFE FOR PICO POPULATION 1: BONE AND SOFT TISSUE TUMOURS?

> **Are there clinical harms associated with PBT intervention in adults with bone or soft tissue cancers such as chordomas and spinal/paraspinal sarcomas? If so, is PBT comparatively safer than alternative oncotherapies for bone and soft tissue cancers in adults?**

There are significant gaps in the published clinical data, especially on harms associated with PBT treatment of patients with spinal/paraspinal soft tissue sarcomas such as chondrosarcomas and rhabdomyosarcomas. The CADTH HTA report (2017)[22] identified no SRs published between 2007 and 2017 detailing clinical harms associated with PBT use on bone cancers.

Toxicities related to specific cancer types

Irradiation of clival chordomas is often associated with neurocognitive side effects given the close proximity of these tumours to OARs such as the brainstem. Fossati et al (2016)[23] reviewed case series published between 1999 and 2014 and identified in three out of seven original independent studies, moderate to severe late optic neuropathy occurrences in 2-9% of skull base chordoma and chondrosarcoma patients treated with passive scattering or pencil beam PBT. Hearing loss was also identified in as much as 67% of chordoma patients receiving passive scattering PBT over the cochlear.

Acute and late radiation-related toxicities

For patients with bone tumours of the axial skeleton, further study is required beyond single-arm case series in order to better understand and compare the acute and late complications resulting from PBT, PRT or other cancer treatment modalities like chemotherapy or surgery. The Inst.CER HTA report (2014)[7] noted that in patients with primary or recurrent sacral chordomas, and receiving PBT and/or PRT alone, a slightly higher rate of bowel or bladder dysfunction was observed compared to patients who were surgically treated in combination with adjuvant PBT and/or PRT.

One comparative cohort study looked at the risk of post-operative wound healing complications occurring after RT in either patients receiving combined PBT with PRT prior to and after surgical resection of chordomas or patients treated only post-operative combined PBT and PRT[30].

Radiation dose

Mima et al[29] investigated differences in the therapeutic potential of PBT or CIT in adults with primary chordomas of the sacral spine. Both modes of particle therapy were delivered at 70.4 Gy over 14 fractions or 32 fractions. Differential fractionation of dose delivery of neither PBT nor CIT impacted on local tumour control, overall survival or disease progression. In another comparative study assessing PBT monotherapy versus combined PBT with PRT radiotherapy, fractions given twice daily or once per day did not affect local tumour control of spinal chordomas and chondrosarcomas at four years post-treatment (59% versus 59%, p=0.96)[31].

A summary of the comparative safety of PBT in bone cancer patients is provided in Table 12. Upon further review, no trials provided a sufficient comparison for the safety of PBT to comparators. This was due to these studies being unable to demonstrate the specific effect of PBT.

IS PBT SAFE FOR PICO POPULATION 2: OCULAR TUMOURS?

> **Are there clinical harms associated with PBT intervention in adults with ocular melanomas? If so, is PBT comparatively safer than with alternative oncotherapies against tumours of the eye?**

There are key risks associated with RT treatment of ocular tumours that are commonly considered across all studies. These include the development of RT-related glaucoma, cataracts, and maculopathies.

Acute and late radiation-related toxicities

Verma (2016) conducted a review of fourteen original case series, where radiation-related toxicities were relatively high and enucleation required for up to 25% of patients who had undergone PBT. A rate of 27-38% of PBT patients experienced retinal detachment, as well as glaucoma (11-29%), cataract development (31-62%) and vitreous haemorrhaging (9-14%). Comparison of harms between PBT and other cancer therapies were not covered.

The Inst.CER HTA (2014) identified an RCT comparing combined PBT with thermotherapy to PBT monotherapy in 151 patients with uveal melanoma (Desjardins, 2006). No significant differences were observed in the incidence rates of maculopathy, pappilopathy, glaucoma or cataracts between the two comparative treatment arms. In a more recent study of choroidal melanoma patients, those receiving adjuvant PBT with surgical endoresection showed a mild reduction in incidence rates of both secondary glaucomas and cataracts relative to patients treated with PBT alone[32]. 10-40% of PBT monotherapy patients presented with late glaucoma after 24 months post-radiotherapy, and/or secondary cataracts after 12 months of follow-up.

Radiation dose

Fractionation of dosage is integral to radiotherapy treatment plans as a single treatment session of high dose irradiation can result in the development of significant toxicities. Interestingly, choroidal melanoma patients receiving four repeated 14.6 Gy fractions of PBT did not display differences in the risk of radiotherapy-related complications when compared to patients treated with a single high dose of photon-based stereotactic radiosurgery (35 Gy)[33].

Table 12 provides a summary of the comparative safety of PBT in patients with ocular tumours relative to other treatment modalities.

IS PBT SAFE FOR PICO POPULATION 3: PAEDIATRIC CANCERS?

> Are there clinical harms associated with PBT intervention in children and adolescent patients with cancers of the CNS? If so, is PBT comparatively safer than alternative oncotherapies against paediatric CNS tumours?

Acute toxicities related to specific cancer types

Radiation-induced intracranial changes, such as encephalopathies and vasculopathies, are common in paediatric patients receiving PBT to the head as a treatment for brain or skull cancers[22, 25, 36, 39, 42]. These changes are routinely detected by diagnostic cranial imaging especially during the acute phase follow-up and can be symptomatic, however not in all cases. PBT intervention did not afford significant advantages over IMRT in three independent studies of comparative cohorts[36, 39, 42]. In fact, in a small-sized investigation of paediatric ependymoma patients, Gunther et al. confirmed grade 3 and 4

intracranial abnormalities 37% of PBT-treated patients compared to no incidences in patients receiving IMRT, however, statistical testing was not conducted[39].

Systemic effects

Endocrinopathies were observed in PBT-treated paediatric cancer patients across multiple studies. However, compared to IMRT or conventional PRT, there are large discrepancies in the literature on whether PBT results in lower, comparable or higher incidence rates of post-treatment hormone deficiencies, hypothyroidism and/or adrenal insufficiency[22, 25, 36, 41].

Song et al[38] also noted significant haematological advantages in PBT treatment for various paediatric brain tumours. The incidence of acute grade 3 and 4 thrombocytopenia was markedly lower PBT-treated patients (20% and 3 %) compared to children who received PRT (31% and 23%, p=0.042).

Secondary malignancies

Laprie et al[24] reviewed the incidence of secondary malignancies in a highly heterogenous paediatric cohort with various types of primary tumours, ranging from cancers of the CNS and axial skeleton to genitourinary neoplasms as well as lymphomas of the arm. No significant difference was observed in the rate of secondary malignancies post-radiotherapy between 44 PBT patients and 44 PRT patients as part of a larger adult study population. However, a 3.3% mild reduction in the secondary malignancy incidence rate was observed in PBT patients over children receiving photon-based treatment (p=0.085). The median time taken for the development of second cancers post-treatment was 6 years in the PBT cohort and 4.75 years in the PRT cohort.

For paediatric patients with retinoblastoma, various studies including the CADTH HTA report, Leroy et al[25], and Sethi et al[35] documented a favourable reduction in the risk of secondary malignancies with PBT treatment over photon-based treatment plans. In these studies, the 10-year cumulative incidence of RT-induced or in-field secondary malignancies was significantly different, reported at 0% for PBT-treated children versus 14% for PRT-treated children (p = 0.015). Near identical findings on the incidence of secondary malignancies are also reported with historical studies mentioned in Section C3.

Table 12 summarises the safety risks associated with PBT use for childhood CNS tumours, comparing safety risks between PBT and PRT or IMRT.

Radiation dose

In a study of PBT or CIT-treated children with medulloblastoma, Eaton et al. confirmed that craniospinal radiation dose was a significant factor for the development hypothyroidism post-radiotherapy (p=0.037), irrespective of the mode of radiotherapy. Conversely, in the same study there was no relationship found between radiation dose and adrenal insufficiency[41]. Equally, Eaton et al. performed multivariate analyses and deducted that craniospinal radiotherapy dosage was not found

to correlate with recurrence-free survival rates in paediatric medulloblastoma patients (hazard ratio= 0.83, p=0.096)[40].

Laprie et al[24] conducted a systematic review on the use of PBT versus PRT in paediatric patients with CNS tumours and reported on potential health benefits afforded by the two radiotherapies. It was noted that the dosimetric accuracy of PBT reduces unnecessary radiation exposure to critical OARs such as the pituitary gland, where doses more 18 Gy can result in growth hormone deficiency and doses above 40 Gy can disrupt thyroid stimulating hormone and adrenocorticotropic hormone regulation. Similarly, auditory and visual structures display a sensitivity threshold to radiation doses above 35 Gy and 59 Gy, respectively.

IS PBT SAFE FOR PICO POPULATION 4: OTHER PICO POPULATIONS?

> **Are there clinical harms associated with PBT intervention in patients with nephroblastoma or adenoid cystic carcinoma of the lacrimal or salivary glands? Is PBT comparatively safer than alternative treatments for adults with such malignancies?**

No comparative studies reporting clinical outcomes of PBT intervention of nephroblastoma patients were identified. There were also no HTAs or SRs covering the comparative clinical harms for PBT and other cancer treatment modalities used on adults with adenoid cystic carcinomas of the lacrimal or salivary glands. High quality clinical evidence on PBT use for PICO 4 is severely lacking.

Acute and late radiation-related toxicities

In a comparative study of PBT or CIT intervention in adults with adenoid cystic carcinoma, Takagi et al. detected no significant difference between differentially treated cohorts with respect to the incidence of various grade 3 or more late toxicities, such as mucositis, brain necrosis, vision or hearing perturbations[43]. Conversely, Romesser et al. noted that in adults with salivary gland carcinomas, grade 2 or more acute mucositis in PBT-treated patients occurred only a third of the rate observed in patients receiving CIT (p=0.019)[44]. There were also significant reductions in the incidence of acute nausea (p=0.003) and dysgeusia (p<0.001) among patients of the PBT treatment arms.

A summary of safety outcome measures from comparative studies is provided in Table 12.

Radiation dose

Romesser et al. reported that for patients who underwent PBT for parotid salivary gland carcinomas, significantly lower maximum doses were observed for OARs like the brainstem (0.62 GyE) and spinal cord maximum (1.88 GyE) compared to IMRT (29.7 Gy and 36.3 Gy, respectively, p<0.001 at both sites)[44]. Sparing of these critical organs was not further investigated, however, undetectable radiation dosage to the contralateral parotid and submandibular glands in PBT patients (0 Gy at both sites) versus 1.4 Gy (p<0.001) and 4.1 Gy (p<0.001) to the respective salivary glands in IMRT patients was found to clinically translate into significant mitigation of symptomatic radiotherapy-related acute toxicities, mentioned above.

Table 12   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					
No trials reported					
PICO 2: Ocular cancers					
	retinopathy	PBT 31/106 (29%)	SRS 20/85 (24%)	5.7pp, 17.5	1.2, NR
Sikuade M.et al. (2015)	optic neuropathy	PBT 14/106 (13%)	SRS 23/85 (27%)	13.9pp, 7.2	0.5, NR
	glaucoma	PBT 5/106 (5%)	SRS 9/85 (11%)	5.9pp, 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%)	12.9pp, 7.75	0, p=0.015
	vascular injury	PBT 2/21 (10%)	IMRT 3/31 (10%)	0pp, NA	1, NS
	visual dysfunction	PBT 1/21 (5%)	IMRT 4/31 (13%)	8pp, 12.5	0.38, NS
CADTH (2017), Leroy R. et al. (2016), Bishop A.J. et al. (2014)	hypothalamic obesity	PBT 4/21 (19%)	IMRT 9/31 (29%)	10pp, 10	0.66, NS
	panhypopituitarism	PBT 7/21 (33%)	IMRT 17/31 (55%)	22pp, 4.5	0.6, NS
	endocrinopathies (growth or sexual hormone deficiency, hypothyroidism, adrenal insufficiency)	PBT 9/21 (43%)	IMRT 7/31 (23%)	20pp, 5	1.9, NS
	grade 3 or 4 acute leukopenia	PBT +/- chemotherapy 16/30 (53.3%)	PRT +/- chemotherapy 10/13 (76.9%)	23.6pp, 4.2	0.7, NS
	grade 3 or 4 acute thrombocytopenia	PBT +/- chemotherapy 7/30 (23.3%)	PRT +/- chemotherapy 7/13 (53.8%)	30.5pp, 3.3	0.43, p=0.012
Song S. et al. (2014)	grade 3 or 4 acute dysphagia	PBT +/- chemotherapy 14/30 (46.7%)	PRT +/- chemotherapy 2/13 (15.4%)	31.3pp, 3.2	3, NS
	acute neurological disorders	PBT +/- chemotherapy 4/30 (13.3%)	PRT +/- chemotherapy 3/13 (23%)	9.7pp, 10.3	0.58, NS
	acute ophthalmic disorders	PBT +/- chemotherapy 2/30 (6.7%)	PRT +/- chemotherapy 1/13 (7.7%)	1pp, 97.5	0.87, NS
Gunther J.R. et al. (2015)	grade 3 or 4 intracranial abnormalities (haemorrhaging,	surgery before chemotherapy + PBT	surgery before chemotherapy + IMRT	37.5pp, 2.7	NA, NR

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)
	encephalomalacia or focal necrosis)	6/16 (37.5%)	0/6 (0%)		
Eaton et al. (2016)	hypothyroidism	surgery + chemotherapy + PBT 9/40 (22.5%)	surgery + chemotherapy + PRT 24/37 (64.9%)	42.4pp, 2.3	0.35, p<0.001
	growth hormone deficiency	surgery + chemotherapy + PBT 21/40 (52.5%)	surgery + chemotherapy + PRT 21/37 (56.8%)	4.3pp, 23.5	0.93, NS
	adrenal insufficiency	surgery + chemotherapy + PBT 2/40 (5%)	surgery + chemotherapy + PRT 3/37 (8.1%)	3.1pp, 32.2	0.62, NS
	sex hormone deficiency	surgery + chemotherapy + PBT 1/40 (2.5%)	surgery + chemotherapy + PRT 7/37 (19%)	16.4pp, 6.1	0.13, p=0.025
	precocious puberty	surgery + chemotherapy + PBT 7/40 (17.5%)	surgery + chemotherapy + PRT 6/37 (16.2%)	1.3pp, 77.9	1.1, NS
Sato et al (2017)	intracranial vasculopathy	surgery + PBT 3/41 (7.3%)	surgery + IMRT 5/38 (13.2%)	5.8pp, 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%)	26.1pp, 3.8	1.4, p=0.019
	grade ≥2 acute mucositis	PBT 3/18 (16.7%)	IMRT 12/23 (52.2%)	35.5pp, 2.8	0.32, p=0.019
	grade ≥2 acute nausea	PBT 2/18 (11.1%)	IMRT 13/23 (56.5%)	45.4pp, 2.2	0.2, p=0.003
	grade ≥2 acute dysgeusia	PBT 1/18 (5.6%)	IMRT 15/23 (65.2%)	59.6pp, 1.7	0.09, p<0.001
	grade ≥2 acute dysphagia	PBT 1/18 (5.6%)	IMRT 2/23 (8.7%)	3.1pp, 32.2	0.64, NS

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

IS PBT EFFECTIVE FOR PICO POPULATION 1: BONE AND SOFT TISSUE TUMOURS?

> **How does the clinical effectiveness of PBT compare to alternative treatment modalities for adults with craniospinal tumours and paraspinal sarcomas?**

Overall survival and local tumour control were the two main outcome measures investigated in systematic reviews on PBT use in adults with chordomas and chondrosarcomas[1,6,7,10].

Overall survival

Matloob et al. found that for clival chordomas patients, overall survival rates after 5 years post-treatment with 67 Gy of combined proton and photon RT (80.5%) were comparable to independent cohorts receiving PBT (80% with 50-80 Gy dosage)[26]. Parallels findings were also noted in original retrospective comparative cohort studies where there were no significant differences in the overall survival of patients prescribed with PBT treatment plans versus those who had undergone resection surgery of the tumour[28], or those patients treated with CIT[29].

Local tumour control

In terms of local tumour control in adult cases of chordomas and chondrosarcomas, PBT did not offer significant improvements when compared to CIT 3 years after treatment[29], or IMRT after 4 years of follow-up[31].

Table 13 summarises health benefit outcomes of PBT use for bone cancers. However on further investigation, no trials (provided in Table 11) provided a sufficient comparison for the effectiveness of PBT to comparators. Three studies (Molina et al., 2014[28], Rotondo et al., 2015[30], Indelicato et al., 2016[31]) did not allow for the effect of PBT to be evaluated while the last study (Mima et al., 2014[29]) compared PBT with carbon ion therapy; a new form of particle therapy of uncertain effectiveness.

IS PBT EFFECTIVE FOR PICO POPULATION 2: OCULAR TUMOURS?

> **How does the clinical effectiveness of PBT compare to alternative treatment modalities for ocular melanomas in adult patients?**

Overall survival

The patient survival outcomes for PBT use in patients with ocular melanomas are largely incoherent or not statistically validated in the literature.

A review of two independent comparative cohort studies in the CADTH HTA (2017) highlighted that PBT treatment of chordoidal melanomas in adults is associated with higher mortality (9.4%) compared to iodine-125 brachytherapy (3.7%) or ruthenium-106 brachytherapy (5%), with no statistical testing results[22]. Expert advice suggests that PBT may have been used to treat larger melanomas than for brachytherapy, which may account for the higher mortality. Findings from the Inst.CER HTA (2014) point to PBT treatment of recurrent uveal melanomas being beneficial, resulting in significantly higher overall survival (63%) compared to enucleation (36%), p=0.04[7]. In contrast, Sikuade et al showed no difference in in overall survival of choroidal melanoma patients receiving PBT or photon-based stereotactic radiosurgery[33].

Local tumour control

Based on primary studies of clinical data from patients with recurrent ocular melanomas, enucleation rates due to local tumour recurrence after primary PBT treatment was higher in patients receiving secondary surgical procedures such as endoresection (42.1%) and endrodrainage (20%), than patients treated only with primary PBT (4.7%)[34].

In contrast, choroidal melanoma patients receiving PBT monotherapy showed comparable local tumour control rates to PBT patients with additional endoresection, with single incidence local recurrences observed in each treatment study arm[32].

Freedom from metastasis

In patients with recurrent uveal melanomas, secondary PBT treatment resulted in improved freedom of metastasis rates compared to patients having undergone enucleation (66% versus 31%, respectively, p= 0.028)[7].

Patient-relevant outcomes (visual acuity)

For choroidal melanoma cases, use of PBT favoured the preservation of visual acuity with Snellen scale scores 20/16-20/50 observed in 50% of PBT patients versus in 18.2% of patients receiving combination therapy with PBT and surgery[32]. Parallel results were observed when PBT was compared with stereotactic radiosurgery[33].

Table 13 summarises health benefit outcomes of PBT use for ocular cancers. Upon further review, one trial, Sikuade et al., 2015[33] (provided in Table 11) provided a sufficient comparison for the effectiveness of PBT to comparators.

IS PBT EFFECTIVE FOR PICO POPULATION 3: PAEDIATRIC AND ADOLESCENT CANCERS?

> **How does the clinical effectiveness of PBT compare to alternative treatment modalities for paediatric CNS tumours, and other childhood malignancies such as neuroblastoma and retinoblastoma?**

Overall survival

While there is a lot of coverage in the literature regarding the benefits of PBT for use against childhood brain tumours, PBT was not found to be superior against the use of adjuvant PRT with surgery[40] or with IMRT treatment plans[36, 39, 42] in terms of promoting overall survival of paediatric cancer patients. These findings are also largely reflected both in the ICER and CADTH HTA reports.

Local tumour control

Sato et al. reported a significant improvement in PBT-induced protection against the tumour recurrence compared to combined IMRT and surgical intervention (17% versus 55.3%, p=0.005) in paediatric patients with intracranial ependymoma[42].

Incidence of metastasis

In their retrospective audit to identify secondary non-ocular tumours in paediatric survivors of retinoblastoma, Sethi et al. detected a single occurrence of osteosarcoma in the left distal femur 9 years after primary PBT whereas no distant tumour events were identified in PRT-treated patients[35].

Health-related quality of life (HRQoL)

Yock et al. conducted parent-proxy HRQoL surveys in paediatric cases of brain cancers and found that PBT intervention resulted in significant improvement in quality of life scores (p=0.002) compared to conventional PRT[37]. Total scored were derived from summary scores across five performance domains, including physical and psychological well-being, as well as emotional, social, and school functioning. All domain summary scores were significantly different (p<0.05) between PBT and PRT patients, except school functioning.

Additional information from historical studies on paediatric HRQoL post PBT treatment is provided in Section C3.

Patient-relevant outcomes

Craniospinal irradiation can influence bone growth and/or haematological homeostasis in paediatric cancer patients. Significant advantages with the use of PBT were also reported in comparative studies of PBT versus PRT in children with germinomas, mixed intracranial germ cell tumours, and medulloblastomas; PBT treatment resulted in minimal radiation-related body height perturbations (p=0.02)[41] as well as a reduction in platelet transfusion rates (p=0.042)[38]. Table 13 provides details the effectiveness of PBT in paediatric and adolescent cancers against other cancer treatment modalities. Although published in two different trials, results for Eaton et al., 2016[40, 41] have been combined together as results were more or less obtained from the same trial population.

IS PBT EFFECTIVE FOR PICO POPULATION 4: OTHER PICO POPULATIONS?

> **How does the clinical effectiveness of PBT compare to alternative treatment modalities for nephroblastoma and adenoid cystic carcinoma of the lacrimal or salivary glands?**

Overall survival

Takagi et al. identified a population of eighty adults with head and neck cancer treated with either PBT or CIT (40 each cohort) of which 14 % presented with adenoid cystic carcinomas of the major salivary glands. Despite the overall survival rates not being significantly different between the PBT and CIT treatment arms, the 5-year survival rate was noted as 3.4 times higher in PBT-treated patients over the CIT group[43]. Romesser et al also found no statistically different overall survival rates between patients with salivary gland carcinomas receiving PBT and those treated with IMRT[44].

Local tumour control

Local tumour control measurements were not significantly different when PBT was compared to CIT treatment in adults with adenoid cystic carcinoma[43], or when PBT was compared to IMRT[44]. stereotactic radiosurgery[33].

Table 13 summarises health benefit outcomes of PBT use for ocular cancers. On further investigation, one trial, Romesser et al., 2016[44] (provided in Table 11) provided a sufficient comparison for the effectiveness of PBT to comparators.

Table 13   Results of key effectiveness 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 treat)	Relative difference (relative risk, results of statistical test)
PICO 1: Brain, spinal and soft tissue cancers					
No trials reported					
PICO 2: Ocular cancers					
Sikuade M.J. et al. (2015)	overall survival	PBT 87%	SRS 84%	3pp, 33.3	1.0, NR
	local tumour control	PBT 95%	SRS 98%	3pp, 33.3	1.0, NR
	visual acuity ≥ 6/60	PBT 55%	SRS 33%	22pp, 4.5	1.7, NR
PICO 3: Paediatric and adolescent cancers					
Sethi R. et al. (2014)	freedom from distant secondary malignancies (metastases)	PBT 54/55 (98.2%)	PRT 31/31 (100%)	1.8pp, 55	1, NR
Bishop et al. (2014)	3-year overall survival	surgery + PBT (PSPT) 94.1%	surgery + PRT 96.8%	2.7pp, 37	1, NS
Yock T.I et al. (2014)	HRQoL (mean total score)	PBT 75.9	PRT 65.4	NA	NA, p=0.002
Song S. et al. (2014)	freedom from platelet transfusion	PBT +/- chemotherapy 25/30 (83.3%)	PRT +/- chemotherapy 7/13 (53.8%)	29.5pp, 3.4	1.5, p=0.042
Gunther J.R et al. (2015)	4-year overall survival	surgery + chemotherapy + PBT NR/37 (87.5%)	surgery + chemotherapy + IMRT NR/35 (78.8%)	8.7pp, 11.5	1.1, NS
Eaton B.R. et al. (2016)	6-year overall survival	surgery + PBT 82%	surgery + PRT 87.6%	5.6pp, 17.9	0.9, NS
	6-year local tumour control	surgery + PBT 95%	surgery + PRT 76.5%	18.5pp, 5.4	1.2, NS
	body height changes	surgery + PBT -1.19	surgery + PRT -2.0	NA	NA, p=0.02

Study	Outcome	Intervention* n with event/N (%)	Comparator n with event/N (%)	Absolute difference (risk difference, number needed to treat)	Relative difference (relative risk, results of statistical test)
	(mean score)				
	BMI changes (mean)	0.6	0.38	NA	NA, NS
Sato M. et al. (2017)	3-year overall survival	surgery + PBT 97%	surgery + IMRT 81%	16pp, 6.3	1.2, p = NS
	3-year progression free survival	surgery + PBT 82%	surgery + IMRT 60%	20pp, 4.5	1.4, p = 0.031
	recurrence rate	surgery + PBT 7/41 (17%)	surgery + IMRT 21/38 (55.3%)	38.2pp, 2.6	0.3, p = 0.005
PICO 4: Other PICO-relevant cancers					
Romesser P.B. et al. (2016)	1-year overall survival	PBT 83.3%	IMRT 93.3%	10pp, 10	0.9, NS
	1-year local tumour control	PBT 80%	IMRT 95.5%	15.5pp, 6.5	0.8, NS
	freedom from metastasis	PBT 16/17 (94%)	IMRT 17/21 (81%)	13.2pp, 7.6	1.2, NS

Abbreviations: BMI, body mass index; IMRT, intensity modulated radiotherapy; NA, not applicable; NR, not reported; NS, not significant with p>0.05; PICO, Abbreviations: PICO, patients intervention comparator outcomes; PBT, proton beam therapy; pp, percentage points; PRT, photon radiotherapy; PSPT, passively scattered proton therapy; SRS, stereotactic radiosurgery

Note: *When stated, the type of PBT administered, i.e. passively scattered proton therapy or intensity modulated proton therapy has been provided.

B.7.   INTERPRETATION OF THE CLINICAL EVIDENCE

The evidence base for the current clinical evaluation of PBT is largely comprised of primary data from comparative cohort studies, each detailing at least one patient outcome measure of clinical effectiveness of PBT in contrast to other common radiation modalities. Case series or similar trial studies with a single treatment arm were not considered in this assessment. Primary studies and the range of outcome measures included in the evidence base are listed in Table 11 and Appendix C.

ON THE AVAILABILITY OF EVIDENCE

Data on the safety and effectiveness outcomes of PBT from prospective RCTs are severely lacking in the literature. In contrast, there is a large number of single-arm studies or case series assessing PBT outcomes with no comparator controls. It is expected that as clinical trials progress in the coming years (listed in Section F2), new data should add better resolution to our understanding of the net benefits of PBT in oncology.

There was inadequate coverage on the use of PBT in various PICO-defined cancer populations, particularly in patients with nephroblastoma and paraspinal soft tissue sarcomas such as liposarcomas, fibrosarcomas, and rhabdomyosacoma.

In terms of PICO-defined patient outcomes, the safety implications associated with different radiation doses of PBT and of its radiotherapy comparators are not thoroughly investigated across all studies. On the most part, comparative cohort studies of PBT versus alternative cancer therapies were designed with matched radiation dosage and fractionation plans which enabled direct comparisons of patient health outcomes. Additionally, there is insufficient data on the HRQoL from patient cohorts receiving PBT versus other treatment alternatives.

ON THE QUALITY OF EVIDENCE

The included studies in this Assessment Report are predominantly comprised of retrospective comparative cohort research. Severe limitations in the quality of evidence and a high risk of bias are intrinsic to the retrospective comparative cohort design, especially with allocation concealment and/or blinding. Additionally, a substantial level of heterogeneity in patient and tumour characteristics was apparent within some study cohorts. These confounding factors further add to the risk of bias in results. For instance, 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. This was especially the case in studies of PBT treatment of head and neck cancers, where analyses were often performed on a pool of patients treated for a range of different tumour classes.

Heterogeneity in results across similar studies reporting on the same outcome measure was expected with independent research. These inconsistencies between findings of individual studies were minimal and likely a result of unique study sites. In a number of studies, however, the use of a small sample size may have influenced findings inconsistent with the rest of the literature, since it does not afford reliability and statistical power in results. A small sample size was unsurprising for PBT studies in patients with rare cancers such as childhood cancers.

ON THE COMPARATIVE SAFETY AND EFFECTIVENESS OF PBT OVER ALTERNATIVE THERAPIES

To evaluate the net therapeutic impact of PBT over treatment alternatives for each PICO population, the magnitude of the effect, relative difference and statistical difference of benefits (Table 13) over harms (Table 12) were carefully considered.

Further high quality primary research is needed to assess the use of PBT for PICO 1 cases. For therapeutic use on brain tumours or sarcomas of the axial skeleton, the clinical data overall demonstrated that PBT was comparable to alternative therapies such as IMRT or CIT. This observation was paralleled in the safety outcome measures, where PBT did not present a statistically significant decrease in incidence of harms. Taken together, PBT therefore does not represent a significant step forward in the treatment of brain and spinal cancers.

There is substantial coverage on the use of PBT for PICO 2 ocular melanomas in the literature. The current clinical evaluation found that PBT treatment preserved visual acuity compared to surgical resection or photon-based radiosurgery. However, PBT was not superior to these alternative therapies

in regards to the prevention of radiation-related toxicities to the targeted eye. An incremental increase in the incidence of glaucomas and retinopathies were associated with PBT treatment of ocular melanomas. With these safety concerns, and given the lack of any difference in local tumour control or overall survival afforded by PBT treatment of patients compared to surgical intervention, PBT should not be considered as the first option for treatment of ocular melanomas.

In the case of PICO 3 paediatric cancers, particularly tumours of the CNS, there is a body of clinical evidence pointing to PBT as a superior mode of treatment relative to photon-based RTs. The effectiveness of PBT over alternative RTs was reflected in its capacity to directly control tumour growth, progression and/or recurrence after primary treatment. These benefits were balanced with reduced harms in PBT-treated patients, including protection against certain RT-induced endocrinopathies, haematological abnormalities, and visual dysfunction. Further improvement to the quality of available clinical data is warranted, particularly with the lack of large scale RCTs, however there may be ethical concerns regarding the allocation of children into non-PBT treatment regimens and denied the net benefits of PBT.

There is insufficient evidence to evaluate the safety and effectiveness of PBT as an intervention for nephroblastoma patients or cases of adenoid cystic carcinoma. Major inconsistencies in the evidence base are identified in regards to both the incidence rates of harms grade 2 or more, as well as measures of treatment effectiveness, namely overall survival of patients and local tumour control. It is critical for more clinical research be conducted in this area.

Table 14 summarises the therapeutic profiles of PBT according to patient-relevant outcomes observed in specific PICO populations.

Table 14 **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	0	NA – no evidence identified	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

Outcomes for PICO populations	Number of studies	Quality of evidence (GRADE)[a]	Relative to primary comparators
Effectiveness for PICO 4: Other populations	1	⊕⊙⊙⊙	Uncertain

Abbreviations: GRADE, Grades of Recommendation, Assessment, Development and Evaluation; PICO, patients intervention comparator outcomes.

[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.

SECTION C   TRANSLATION ISSUES

C.1.   OVERVIEW

This section presents translation issues identified to connect the clinical evidence discussed on the comparative effectiveness of PBT in Section B to the economic evaluation presented in Section D.

The question to be answered in an economic evaluation of PBT are "How do the cost and outcomes associated with PBT compare with the cost and outcomes associated with alternative therapies (such as PRT and plaque brachytherapy) for the patients treated in the PICO population?" We discuss the methodological and evidence requirements, the translational issues, necessary to model such an analysis here.

The challenge of economic evaluation of PBT is primarily due to the uncertainty about the outcomes of PBT relative to alternative therapy (PRT, plaque brachytherapy). A realisation of these limits guides our evaluation. There is a scarcity of evidence in the target populations in the PICO directly comparing the effectiveness and safety of PBT with relevant alternative therapies.

The scarcity of evidence is made explicit by referencing existing technology assessments of PBT on the quality of available evidence. These assessments measure the outcomes from PBT in cancer populations, which include the sub-populations outlined in the PICO. As an overview, it is useful to refer to some assertions about the state of the evidence on comparative effectiveness and cost-effectiveness of PBT made in three of these reviews.

Review #1:

In a March 2014 technology assessment of PBT by the Washington State Health Care Authority in the USA, reported that "The level of comparative evidence was extremely limited for certain conditions and entirely absent for others."[P33] And for ocular tumours, adult brain/spinal tumours, paediatric cancers, and liver, lung, and prostate cancers "the strength of evidence was low or moderate for all of these conditions. We determine the evidence base for all other conditions types to be insufficient to determine net health benefit."[P33] Further, in summary, "evidence of PBT's comparative clinical effectiveness and comparative value is lacking for nearly all conditions under study in this review…It should be noted, however, that we made judgements of comparability based on a limited evidence base that provides relatively low certainty that PBT is roughly equivalent to alternative therapies."[P64][2] Table 15 summarises the evidence from this review.

Table 15   Washington State Health Technology Assessment on PBT Evidence Summary

Cancer	Net health benefit versus comparators	Type of net health benefit	Strength of the evidence
Ocular	Superior	Benefit ↑, Harm ↓	++
Brain/spinal	Incremental	Benefit =, Harm ↓	+

Cancer	Net health benefit versus comparators	Type of net health benefit	Strength of the evidence
Paediatric	Incremental	Benefit =, Harm ↓	++
Head/neck	Insufficient		+
Other	Insufficient		

Source: Washington State Health Care Authority Final Evidence Report 2014 [45]
Abbreviations: PBT, proton beam therapy.
Notes: This table has been modified from the original.
Strength of Evidence: Low=+; Moderate=++; High=+++; No evidence=0

Review #2:

In May of 2016, in a Rapid Response Report the Canadian Agency for Drugs and Technologies in Health concluded that "Comparative evidence is limited and it is unclear how PBT fits into the landscape of other available therapies, or what the most appropriate indications are." [P2] "There are concerns regarding the quantity, quality and generalisability of the available evidence."[P3] And, "In conclusion, the evidence assessed in this review suggests that the benefit, harms, and cost-effectiveness of PBT versus photon radiotherapy alternatives remain largely unclear."[P17] [46]

Review #3:

The conclusions of the CADTH HTA of August 2017 state "Findings from the clinical review, based mostly on low-quality evidence stemming from poor-quality primary studies, suggest that the clinical effectiveness of PBT, alone or in combination with PRT, is comparable to other types of radiotherapy (RT) in most of the types of cancer included in this overview, with the exception of: greater benefits in meningioma and subgroups of malignant meningioma and poorly-differentiated tumours of prostate cancer in adults; lower benefits in some intramedullary spinal cord glioma in both children and adults, analysed together; and both greater and lower benefits in eye cancer in adults. The safety of PBT alone or in combination with photon RT, compared with other types of RT, varies by the type of cancer and is associated with: greater harms in breast cancer and prostate cancer in adults; lower harms in retinoblastoma in children and medulloblastoma in adults; and both greater and lower harms in oesophageal cancer, optic nerve sheath meningioma, and lung cancer in adults. Nevertheless, the authors of the SR included in the overview caution that the quality of the included primary studies is mostly too low or insufficient to make definitive conclusions about the benefits or harms of PBT." [47]

Incorporating new information into our systematic review does not substantially alter the findings of these reviews. The quality of the reviews was good, and the recommendations were acknowledged. Only a modest amount of new evidence was found and is included in this Assessment Report.

Assessing Cost-Effectiveness

The ability to accurately assess the cost-effectiveness of PBT is greatly limited by the absence of high quality clinical evidence, particularly long-term outcomes, and the uncertainty about actual costs. In a May 2016 a SR of the cost-effectiveness of PBT, Verma states that "studying the cost-effectiveness of PBT is difficult, in part because there is a great reliance on clinical outcomes and toxicity data, and

there is a clear dearth of such data for PBT." [48][P1483] Published economic evaluations largely rely on modelled outcomes from uncontrolled clinical studies.

The optimal method to estimate cost-effectiveness, according to the MSAC Guidelines, is to use evidence comprised of aggregation of results from RCTs. In addition to this, the estimation method should use cost data specific to the choice of therapy delivered that derives from resources employed and measured empirically. The analysis of PBT here deviates from an optimal analysis in many ways for reasons of applicability, extrapolation and transformation issues. These issues are described in Table 16.

Table 16   Translation issues identified in preparing the economic evaluation

Translation issue	Comments
Applicability issues	
Population and circumstances of use	Studies were identified for the PICO population including cranial spinal tumours, ocular melanoma and paediatrics. There are assessments of sub-populations that were not pre-specified. Limited clinical evidence was found for Wilms tumour.
	The quality of the overall clinical evidence is low, mostly consisting of level III evidence. Patient characteristics in the studies have often not been well defined. The clinical evidence base has included populations from the United States, Europe and Asia, often in single centres. No Australian studies have been conducted, and the Australian population is not directly comparable to the populations studied.
	It has not been possible to pool or use meta-analysis for outcomes due to the lack of exchangeability of the PBT clinical evidence, including efficacy and safety, in the PICO populations.
	The heterogeneity of the clinical evidence is high within individual studies due to data being collected retrospectively. Not only is the risk of bias high, patient differences in characteristics, dose fraction difference and collections from different time periods has resulted in variable outcome measures and dosage fractions within studies. The results are therefore not generalisable to the Australian population.
	There is a scarcity of publications that directly compare PBT with relevant alternative therapies including IMRT in the population that would be eligible for public funding under the proposed listing. Nonetheless, the link between the population of the requested listing and the economic model presented in Section D is discussed.
Extrapolation issues	
Progression free survival Overall survival & local recurrence rates	The low quality clinical evidence, and high risk of bias has made it difficult to draw conclusions regarding overall survival, progression rates and local recurrence rates. Further complication results from clinical outcomes reported for multiple populations in the survival evidence. Published health economic models that have assessed the cost-effectiveness of PBT have sourced data from low level clinical evidence or literature based assumptions relating to alterative modalities.
Secondary malignancies	Limited information is available for secondary malignancies of low quality for patients in the PICO population.
Adverse events	While theoretically beneficial, the clinical values have not been demonstrated from the increasing number of patients treated with PBT. Limited comparative long-term safety information is available for PBT in the PICO population.
Transformation issues	
Utility weights applied to the economic model	Comparative quality of life data is limited for PBT. In addition, The Paediatric Quality of Life instrument cannot be mapped to the utilities in the paediatric PICO population.
Healthcare resource use and associated costs	Evidence on costs relating to particle therapy and on treatment lengths relevant for Australian patients is limited.

Abbreviations: PICO, patient intervention comparators outcomes; PBT, proton beam therapy; IMRT, intensity modulated radiation therapy

C.2. APPLICABILITY TRANSLATION ISSUES

A number of studies were identified for the PICO population including cranial spinal tumours, ocular melanoma and paediatrics. Due to the nature or rare cancers it was often required to assess sub-populations of studies that were not pre-specified.

The clinical evidence is level III and IV evidence. No Australian studies have been conducted. The clinical evidence base has included populations from the United States, Europe and Asia, often in single centres and therefore the populations studied, are not directly comparable to the Australian population.

Due to the lack of exchangeability of the PBT clinical evidence, it has not been possible to pool or use meta-analysis for outcomes, including efficacy and safety, in the PICO populations.

The heterogeneity of the clinical evidence is high within individual studies due to data being collected retrospectively. Not only is the risk of bias high, patient differences in characteristics, dose fraction difference, and evidence collections from different time periods has resulted in variable outcome measures and dosage fractions within studies. The results are therefore not generalisable to the Australian population.

There is a scarcity of publications that directly compare PBT with relevant alternative therapies including IMRT in the population that would be eligible for public funding under the proposed listing. Nonetheless, the link between the population of the requested listing and the economic analysis presented in Section D is discussed.

C.3. EXTRAPOLATION TRANSLATION ISSUES

DEMAND FOR PBT IN AUSTRALIA

The HealthPACT Overview of Proton and Heavy Beam Radiation states that

> The economic analysis of an Australian proton beam facility would need to consider current and future patient demand. Current patient demand within Australia and New Zealand is entirely dependent on the accepted range of clinical indications where PBT would be considered superior to other potential treatments. Until dedicated modelling is undertaken, the potential domestic demand for this treatment modality is difficult to estimate. The current indications where the evidence base supports the use of PBT include ocular tumours, tumours located proximal to the base of skull, including chordoma and chondrosarcomas, primary or metastatic tumours of the spine where spinal cord tolerance may be exceeded with conventional treatment, and selected paediatric tumours. The number of Australian and New Zealand patients with these indications, who would require PBT, remains small. [6]

The HealthPACT report used the results of a 2014 estimation of the utilisation rates of radiation therapy by tumour type in the Australian Nuclear Science and Technology Organisation (ANSTO) recommendations to arrive at their own estimation of the demand for PBT. That estimate is shown in Table 17.

Table 17   **2014 ANSTO estimation of Australian patients eligible for particle therapy using nine indicators**

Indication	Incidence in 2014		Candidates for conventional radiotherapy		Candidates for particle therapy	
	All patients	Paediatric patients	All patients	Paediatric patients	All patients	Paediatric patients
Brain/CNS	1,773	138	1,418	110	709	110
Head and neck/skull	2,609	16	1,931	12	913	13
Ocular	271	23	271	23	190	23
Lung	6,883	2	5,506	2	619	2
Prostate	20,914	0	12,130	0	837	0
Liver	1,402	19	0	0	70	10
Bone	199	43	0	0	100	43
Uterine cervix	830	1	589	1	166	1
Pancreas	2,739	1	1,342	0	274	1
Total	**37,620**	**243**	**23,187**	**148**	**3,878**	**203**

Source: HealthPACT Proton and Heavy Ion Therapy: An Overview January 2017[6]
Abbreviations: ANSTO, Australian Nuclear Science and Technology Organisation; CNS, central nervous system.

OUTCOMES

We have assessed the information on outcomes of PBT and conventional therapy (PRT and brachytherapy) for chordoma of the axial skeleton (defined as the skull, vertebral column and bony pelvis); sarcoma of the axial skeleton; paediatric CNS tumour; ocular melanoma; retinoblastoma; soft tissue sarcoma in close proximity to the axial skeleton (to include rhabdomyosarcoma); adenoid cystic carcinoma of the lacrimal or salivary glands; craniopharyngioma; intracranial germ cell tumour; neuroblastoma; and nephroblastoma.

Patients within the PICO populations with difficult to treat tumours because of location of the tumours are candidates for PBT treatment. The studies of the treatment of these tumours are mostly observational studies with small patient populations. The available evidence from these studies does not allow pooling of patient populations across studies in PICO sub-populations. Clinicians routinely classify the patients according to risk category, yet there is not uniform reporting in the literature on the risk categorisation of the patients treated.

For the purposes of economic evaluation, the PICO populations have been aggregated into three groups. The rationale for this is twofold; first this aggregation is aligned to the findings presented in Section B in terms of evidence and quality of evidence. Secondly, a review of existing cost-effectiveness literature on PBT shows similar aggregation in the cost-effectiveness studies. The PICO

populations aggregated into head/neck, ocular and paediatric categories is explained in Table 18. This in accordance with the evaluation presented in Table 15.

Table 18   **Translation of the PICO Populations between Section B and Section D**

PICO #	PICO Description in Section B	PICO Population	Cost-Effectiveness Groups in Section C
1	Head/skeleton tumours	Chordoma of the axial skeleton (defined as the skull, vertebral column and bony pelvis). Sarcoma of the axial skeleton (including chondrosarcoma) Intracranial germ cell tumour Soft tissue sarcoma in close proximity to the axial skeleton (to include rhabdomyosarcoma). Craniopharyngioma	Head and Neck
2	Ocular tumours	Ocular melanoma	Ocular tumours
3	Paediatric and adolescent tumours	Childhood CNS tumours (including craniopharyngioma, intracranial germ cell tumour, meningioma, gliomas, ependymoma, medulloblastoma) Neuroblastoma Retinoblastoma	Paediatric
4	Other PICO-relevant tumours	Adenoid cystic carcinoma of the lacrimal or salivary glands Nephroblastoma	-

Abbreviations: PICO, patient intervention comparators outcomes

Not all patients diagnosed in the PICO areas can be treated by PBT. Glimelius[49] concluded that 22% of patients with tumours of the brain and other CNS would be appropriate for PBT, and 75% of patients with oral cavity and pharynx would be appropriate for PBT. These are patients with difficult to treat tumours because of location of the tumours. The HealthPACT report includes an estimate of the demand for PBT. They used Australian recommendations on optimal radiotherapy utilisation rates[50] and from this assumed eligibility rates for particle therapy substitution. They used 2009 Australian cancer incidence data, obtained from the Australian Cancer Database, adjusted to the 2014.

There were not any cost-effectiveness studies found exclusively for patients within PICO #4 (adenoid cystic carcinoma of the lacrimal or salivary glands and nephroblastoma). Therefore, no results are discussed in this section.

POPULATION

The estimates contained in Table 19 have been adjusted to the 2017 population for the patient groupings stated in Table 17.

Table 19   **Estimation of Australian patients eligible for particle therapy in 2017 which include all the PICO populations**

PICO #	Cancer	Conventional radiotherapy		Proton Beam Therapy		Difference between PRT & PBT	
	Year	2014	2017	2014	2017	2014	2017
1	Brain/CNS (adults)	1,308	1,377	599	631	709	747
	Head and neck/skull (adults)	1,919	2,021	900	948	1,019	1,073

PICO #	Cancer	Conventional radiotherapy		Proton Beam Therapy		Difference between PRT & PBT	
2	Ocular (adults)	248	261	167	176	81	85
3	Paediatric	148	156	203	214	-55	-58
	TOTAL	**3,623**	**3,815**	**1,869**	**1,968**		

Notes: Adapted from Table 6 in HealthPACT Proton and Heavy Ion Therapy: An Overview January 2017[6]
Abbreviations: PRT, photon radiation therapy; PBT, proton beam therapy.

For the populations in the PICO, it is estimated that 1,869 patients in 2014 are eligible for PBT and with extrapolation using population growth of 5.3% over 3 years from data from the Australian Bureau of Statistics (ABS), there are 1,968 patients eligible for PBT in 2017. There is estimated to be, in 2017, 631 adult patients in brain/CNS, 948 in head and neck/skull, 176 in ocular, and 214 in paediatric. These are the estimates used in this evaluation.

PROGRESSION FREE SURVIVAL OVERALL SURVIVAL & LOCAL RECURRENCE RATES

The low quality clinical evidence, and high risk of bias has made it difficult to draw conclusions regarding overall survival, progression rates and local recurrence rates. Further complication results from clinical outcomes reported for multiple populations in the survival evidence. Published health economic models that have assessed the cost-effectiveness of PBT have sourced data from low level clinical evidence or literature based assumptions relating to alterative modalities. Clinical outcomes have been reported for all of the PICO populations in the reports of survival evidence. The evidence available is summarised in Section B6.

Secondary malignancies

There has been evidence reported on the incidence of secondary malignancies in patients treated with PBT with a population-based cohort of matched patients treated with PRT in retrospective cohort studies matched by cancer histology, age at radiation treatment, sex, year of treatment and site. The main outcome measure was the incidence of secondary malignancies after radiation. A study by Chung et al with a median of 6.7 years of follow-up found the crude rate of secondary malignancies was 5.2% among the proton cohort (29 patients) vs. 7.5% in photon cohort (42 patients). On multivariable analysis, PRT was associated with a decreased risk of secondary malignancy [adjusted hazard ratio, 0.52 (95% confidence interval, 0.32–0.85), p = 0.009] when compared with PRT. For radiation-related solid malignancies, five or more years after treatment, the incidence rate was nearly identical between the two groups (5.7/1000 person-years in the proton vs 5.8/1000 person-years in the photon group). Notably, solid cancer events within five years of therapeutic radiation are not plausibly attributed to radiation therapy. These results demonstrate that the apparent lower rate of subsequent malignancies in the proton group is driven by a deficiency of malignancies among proton patients in the early follow-up period rather than by an excess of malignancies among photon patients in the late follow-up period.[51] It was concluded that the use of PRT was not associated with a significantly increased risk of secondary malignancies compared with photon therapy.[52]

The 2014 WSHC-Heath technology assessment concluded that in patients with brain and spinal tumours that "Limited, low-quality evidence suggests that PBT is associated with reductions in acute radiation-reduced toxicity relative to photon radiation." In head and neck cancers they state that

"evidence is limited and inadequate to compare the potential harms of PBT relative to other radiation modalities". In ocular tumours the report states that "limited, low quality evidence suggests comparable rates of harm for PBT relative to treatment alternative." And, finally, they report in paediatric cancers, "PBT's theoretical potential to lower radiation induced toxicity to children serves as the comparative evidence base. Comparative studies are lacking, most likely due to lack of clinical equipoise. "[2]

There is not enough evidence to model long-term comparative consequences in relation to secondary malignancies across all patients treated, much less model the consequences in each PICO population. The models used in the cost-effectiveness analyses reported below are specific to with secondary malignancies by use of assumptions about the difference between alternative therapies. This is one of the weaknesses of those models. [52]

The transitional probabilities of local recurrence and post-treatment metastases were reported by Moriarty for the treatment of ocular tumours. These probabilities are applied to the patient population estimated for ocular tumours from the HealthPACT study to get an estimate of the number of patients per year with these outcomes from PBT and conventional therapy (Table 20).

Table 20   Outcomes probabilities of patients treated for ocular tumours and the estimated annual outcomes in Australia

Outcome	PBT	Plaque brachytherapy	Enucleation
Post-treatment LC probability	0.009	0.021	0.002
Patients per year	1.5	3.5	0.34
Post-treatment metastasis (MT) probability	0.039	0.029	0.047
Patients per year	6.5	4.8	7.8
LC after MT probability (five year horizon)	0.061	0.045	0.074
Patients per year	0.4	0.21	0.58

Abbreviations: PBT, proton beam therapy; LC, local recurrence; MT, metastasis.

ADVERSE EVENTS

The clinical values have not yet been demonstrated for adverse events due to tissue damage from the increasing number of patients treated with PBT. Limited comparative long-term safety information is available for PBT in the PICO population. The claim that PBT reduces adverse events and thus reduces the cost of care has not been measured adequately to date. The evidence available is summarised in Section B.6. The economic evaluations reviewed in Section D have adverse events for health states in their modelled analyses. The transitional probabilities from treatment to adverse events were obtained from regression models, or information collected with long-term follow-up from registries of patients, along with expert opinion. In each of the tumour categories evaluated head/neck, paediatric and ocular, the number of adverse events are estimated from a modelled approach using the HealthPACT estimate of the demand for PBT.

Expected adverse events (AEs) in paediatric medullablastoma; an estimation of the probabilities of transitioning to adverse events after PBT and conventional therapy is based on Miralbell[53] and employed in Lundkvist. They include hearing loss, hypothyroidism, osteoporosis, growth hormone deficiency (GHD), nonfatal secondary malignancies and fatal events. These probabilities are applied to the 110 children estimated to have PBT.

Table 21   Childhood medullablastoma - radiation-induced events per 100 patients

Variable	Hearing loss	Hypothyroidism	Osteoporosis	GHD	Nonfatal secondary malignancies	Fatal events
Conventional radiation	11.9	16.3	0.4	17.1	1.2	1.91
PBT	1.4	2.7	0.1	2.0	0.7	0.38
Difference	10.5	13.6	0.3	15.1	0.5	1.53

Source: Lundkvist et al 2005[54]
Abbreviations: GHD, growth hormone deficiency

Head/neck

The proportion of patients who had both xerostomia and dysphagia was calculated using conditional toxicity probabilities from a systematic review and a regression of doses on toxicity.[55]

Table 22   Comparative difference in adverse events from PBT and PRT for head and neck cancers

Endpoint	% AEs for PBT	% AEs for PRT	% Difference
Dysphagia ≥grade 2	6.7	15.0	8.3
Dysphagia ≥grade 3	4.9	7.6	2.7
Xerostomia ≥Grade 2	10.0	19.0	9.0
Salivary duct inflammation ≥ grade 2	4.7	7.6	2.9
Feeding tube dependence	1.3	1.7	.4

Source: Rwigema et al 2017[56]
Abbreviations: AEs, adverse events; PBT, proton beam therapy; PRT, photon radiation therapy
Notes: This table has been modified from the original.

SURROGATE OUTCOMES IN THE PICO POPULATIONS

In the consideration of surrogate outcome evidence in HTA, it is recommended that the acceptance of surrogate outcomes be based on RCT data demonstrating an association between the treatment effect on both the surrogate outcome and the final outcome. If this information is not available, alternatively, a SR and meta-analysis can be used to quantify the association between cytogenic response to overall survival in patients with cancers from observational studies. Life expectancy can then be found by extrapolating long-term survival from the weighted overall survival stratified according to the achievement of complete cytogenic response in patients with cancers. Unfortunately, evaluation of the evidence presented in Section B did not make this approach possible either.

The clinical aims of PBT require the delivery of a radiation that gives a sufficient local tumour control rate with the highest dose possible, given a radiation dose-response relationship. Higher doses are related to better overall survival. But higher radiation dose, particularly with concurrent chemotherapy, is associated with higher levels of toxicity. Therefore, studies predominantly focus on the development of new TPSs to deliver higher doses of radiotherapy to properly defined target volumes. The understanding of PBT use is not to the point where we can generalise a dose that is considered best practice and then analyse best practice to obtain clinical outcomes within the PICO populations. There is no single accepted radiation therapy modality to treat all cancers.

Most of the trials reported are single-arm studies, or retrospective analyses, with many comparing the use of the technology to its own technology at different doses of radiation. There is little evidence from comparisons between groups receiving similar doses of radiation by different methods. However, RCT are required at various PBT centres to examine and evaluate the long-term effects and benefits, so as to establish a strong clinical efficacy and toxicity of PBT. For example, in hypoxic tumours such as head and neck cancer, an Edinburgh RCT comparing fast neutrons (with high RBE) and photons showed that local control was similar but late severe radiation morbidity was significantly higher in the neutron treated patients.[57]

At the clinical level, there is also variation in operational procedure practice. There is variation in the choice of treatment planning and in the radiation therapist's and medical physicist's ability to operate the PBT optimally. The focus of the majority of the literature is to report on improvements, if any, in the delivery of the technology given the trade-off between potential benefit and harm. So the outcomes reported are from various practice patterns and the variation in practice makes it difficult to extrapolate evidence to a surrogate outcome, to QoL metrics, progression free survival, or even survival.

COSTS

Capital costs

Mailhot-Vega in a 2013 article estimates a capital investment of US$140 million for setting up a PBT facility and an average cost of US$40,000 per treatment.[58] In The Netherlands, Peeters et al 2010[59] estimated the capital cost of €139 million for a combined proton/carbon facility, €95 million for a PBT facility, and €23 million for a PRT facility. Italy started outpatient PBT services in 2014, and has treated about 400 patients until March 2015. The fee for a patient for three kinds of treatment (protons or carbon ions) is €12,000 for boost (up to six fractions), €18,000 for radiosurgery (1–3 fractions) and €24,000 for full course. A costing study in Belgium[60] calculated literature based costs (2003-2005) for head/ neck cancers, and the estimated cost of PRT was €11,520 (US$13,939), whereas PBT was more than triple the cost at €39,610 (US$47,928).[61]

The 2017 HealthPACT report[62] used data from the Peeters study (2010) to calculate the costs of a PBT facility. Publicly reported costs (equipment only) were AU$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 annually.[59] Using the Peeters methodology, and by using the costs reported in the HealthPACT report, each room would cost roughly AU$45 million in 2016.

Cost associated with adverse events

It has been speculated that the large investment in a PBT facility would be mitigated by avoiding the costs associated with adverse effects and treatment of the damaged healthy tissue surrounding a tumour, as well as with the long-term consequences of not giving an adequate dose to the actual tumour. These effects on cost have been modelled with rather strong assumptions, and not based on large datasets of treated patients over extended periods of time. These issues are discussed in the review of cost-effectiveness studies in <u>Section D</u>. And the value of the AEs averted by PBT is assessed in the economic evaluation.

Casemix

Another line of argument is that PBT needs to be used in a carefully defined population so that cost-effectiveness will improve by "achieving a balance of PBT-indicated cases and "nonessential" cases". For instance, in the USA it has been reported that "proton accelerators are used for a large number of prostate cancer cases. The cost of proton therapy for prostate cancer is typically about twice as much as conventional radiation there, three times that of surgery, and 4–5 times that of brachytherapy [63] The cost difference between particle and photon therapies is relatively small for lung and prostate cancer, but larger for skull-base chordoma, and head and neck tumours"[64]. However, a US analysis demonstrates how restricting patients to so-called "simple case" (i.e. prostate cancer patients) decreases profitability for a PBT unit.[64]

Technological innovation

Technological innovations to optimise PBT are ongoing at this point, including pencil beam scanning, intensity modulated PBT, image guidance, hypofractionation, and compact units; these will likely further decrease treatment costs. Recent advances in optimising treatment times, proton units, beam energies, and field design can lower average cost. Partially because of these innovations, Medicare payments to doctors in the USA for PBT have been estimated to drop 20% over the next decade. PBT reimbursements already have decreased compared with past levels.[65]

Incremental cost

Incremental cost evidence should reflect the per patient use of resources and a suitable estimate of average cost per treatment made. In the case of PBT in Australia, there is not available cost data estimated for PBT on a per patient basis for each of the cancers collected empirically in the PICO

populations. This is due to the fact that PBT is not yet available in Australia. Evidence of the medical direct cost of PBT from the published literature is reported across countries, and for differing years. The evidence is often poorly described in the literature.

Conversely, the cost of treatment associated with PRT is available for facilities and published cost data is also available. Likewise, activity based costing is available from a Canadian study. No such data is available on Australian patients in Australian hospitals. In this MSAC Assessment Report, the cost of IMRT treatment has been estimated by using the MBS and the base case treatment patterns, and compares this cost, via assumption of similarity, to PBT.

A detailed cost analysis was done at the Indiana University Hospital in 2012. They found that for brain and other CNS tumours that, typically, patients were treated over a course of 35 visits for 45 minutes per visit. For oral cavity and pharynx lesions the typical course was 33 visits for 45 minutes. If these patients were paediatric, the time of treatment was an hour, and 33 visits. If all patients were adult, the maximum daily capacity would be twenty patients per day, 5200 per year. This was the estimated capacity for a one room centre. Capital costs for this centre were estimated at US$4,000 per day. Fully allocated, these costs would be US$200-267 per patient per day. In this analysis, it was stated that "a single gantry treating only complex or paediatric patients would need to apply 85% of its treatment slots simply to service debt."[64] The maximum daily capacity estimate of 3900-5200 patients per year can be compared to the estimated number of cancer patients eligible for particle therapy being 1869, using data from the 2014 ANSTO report (refer to Table 19).

The cost of radiation therapy depends heavily on the investment costs for the radiation equipment. Goitein and Jermann in Switzerland estimated the costs of PBT and PRT, dividing the total cost into operation cost per patient, including fixed business costs. Total costs for PBT were 2.42 times those of PRT. Business costs were 43% of proton and 28% of x-ray cost, with business costs being of PBT technology being 3.63 times that of the PRT technology. [66]

As a PBT unit is operationalised, the appropriate cost to consider, from a societal prospective, on a per patient basis should be the long-run marginal cost, or fully allocated cost, that takes into consideration the fixed cost of putting the unit into service, and the variable cost of treatment of a cancer patient with PBT. The average cost of the patient treated by PBT will vary with the capacity utilisation of the PBT unit. The average cost of PBT will decrease until full capacity is reached. Johnstone states that "A 3-gantry facility treating only complex and pediatric cases would not have enough treatment slots to recoup construction and debt service costs at all. For a 4-gantry centre, focusing on complex and paediatric cases alone, there would not be enough treatment slots to cover even 60% of debt service. Personnel and recurring costs and profit further reduce the business case for performing more complex patients…Absent philanthropy, financing a modern proton centre requires treating a case load emphasizing simple patients (i.e. uncomplicated prostate cancers) even before operating costs and any profit are achieved". [64] In addition, an economic analysis should

consider the redundancy cost to the health system of existing linear accelerators (LINACs), which may be underutilised if patients are shifted to treatment with PBT.

Patient cost

Patients incur differential costs in accessing PBT as compared to alternative therapies. There are patient and family costs incurred in travelling to treatment, in accommodation, and hospitalisation. A course of treatment last from 5-9 weeks and the patient's ability to function outside of the hospital environment will vary within the PRT and PBT populations, as well as across the populations. The proximity of the patient to the treatment facility will affect these costs. Co-morbidity and tumour site and type could affect the costs borne by the patient. Since information on these costs is unavailable), they have not been included in this MSAC Assessment Report.

Average cost of treatment: By assuming similar levels of reimbursement for the alternative therapies and excluding capital costs, the results of this MSAC Assessment Report are biased from a societal perspective. The capital outlay, although, not part of the reimbursement scheme, is tax payer funded. However, this Assessment Report is based on the remand of an application to the MSAC and therefore is concerned with the effectiveness and costs associated with PBT for a population included in the PICO, and thus does not involve the analysis of the investment decision for PBT infrastructure. A payer perspective would not include capital costs and costs borne by the patient.

QUALITY OF LIFE (QOL)

In a review of quality of life measurement in PBT, Verma found only one article on each of skull base, brain, head/neck malignancies, and three in paediatric malignancies treated with PBT that met eligibility criteria. He concluded that "Based on limited data, PBT provides favorable QOL/PRO profiles for select brain, head/neck, lung, and pediatric cancers; measures for prostate and breast cancers were more modest,"[67] and that "Pediatric studies demonstrated improvements in QOL during therapy, with additional increases thereafter."

Paediatric QoL

Patients who are treated for tumours of the CNS with conventional PRT, or cranial radiation therapy (CRT), are at high risk of neurocognitive impairment or dysfunction. Reduction in the dose of CRT, particularly for younger children being treated for medulloblastoma, has been shown to be associated with better long-term cognitive function. PBT represents an emerging alternative to conventional PRT; the primary advantage is the ability to deliver the optimal dose of radiation to the tumour site while reducing the exposure of surrounding healthy tissue.

There are only a few reports that describe HRQoL in survivors of childhood brain tumours, but most suggest that neurocognitive impairment is one of the strongest predictors of poor HRQoL[67]. Kuhlthau assessed HRQoL using the PedsQL core module, brain tumour module, and cancer module (PedsMetrics, College Station, TX) in 142 children with CNS tumours who were treated with PBT.

During a three-year period, HRQoL, as reported by both children and parents, improved to levels close to those reported for healthy children, and above those reported for children with other chronic illnesses. Poorer HRQoL was associated with poorer performance on measures of intellectual function, adding more evidence for the association between neurocognitive late effects and HRQoL. This study provides support for the possibility that reducing neurotoxicity and associated late neurocognitive effects will result in better long-term HRQoL. The study did not assess the trends in HRQoL for children treated with CRT using more conventional PRT and therefore a comparative impact on HRQoL cannot be assessed. In addition, an assessment of neurocognitive function was not performed in a systematic manner for the population, so the association between neurocognitive function and HRQoL remains speculative. [68]

In a study by Yock in 2014, primary prospective HRQoL data were collected on paediatric brain tumour patients and survivors treated with PBT. All study subjects were recruited while receiving PBT at Massachusetts General Hospital (MGH) and provided informed consent. Children between the ages of 2 to 18 and their parents were initially surveyed during treatment and then annually thereafter. All patients were assessed through parent-proxy report versions (PPR, for children age 2 and up) of the PedsQL. Detailed methodology for this cohort was previously published. In this study, the median year of radiation treatment was 2007 with the interquartile range (IQR) of 2006-2007. Parent-proxy HRQoL scores were reported at 3 years for the proton radiation therapy cohort and 2.9 years (median) for the photon radiation therapy cohort. The total core HRQoL score for the proton radiation therapy, photon radiation therapy and normative population differed from one another and was 75.9, 65.4 and 80.9 respectively (p=0.002; p=0.024; p<0.001). The proton radiation therapy cohort scored 10.3 and 10.5 points higher than the photon radiation therapy cohort in the physical (PhSD) and psychosocial (PsSD) summary domains of the total core score (TCS, p=0.015; p=0.001). The proton radiation therapy cohort showed no difference in PhSD compared with the normative population, but scored 6.1 points less in the PsSD (p=0.003). Compared to healthy controls, the photon radiation therapy cohort scored lower in all domains p<0.001).[37]

Weber studied fifteen children undergoing primary ATRT.[69] The study used PedQoL: physical, emotional, social, school, psychosocial, composite measured before PBT and compared with measurement at 2 months post PBT. QoL did not deteriorate at 33 months after PBT. Mean values of QoL scores were reported, without statistical comparisons. They did not assess baseline home/socioeconomic situation. There was an isolated comparison at just 2 months post PBT, making it difficult to interpret regarding long-term QoL. This is mild evidence showing that QoL did not decline after PBT, but there was no comparative evidence generated.

Although the PedsQL is widely used among paediatric patient populations, presently it is not possible to directly use the scores from the instrument to calculate quality adjusted life years (QALYs) for this Assessment Report because it produces summary scores which are not preference-based. Transformation of relevant PedsQL scores for PBT in the paediatric population is not appropriate

because the available HRQoL evidence for PBT is based on a diverse paediatric population of different ages. As discussed, comparative quality HRQoL data is not available for PBT and conventional PRT.

Ocular QoL

No studies were found reporting quality of life associated with local recurrence or metastasis of intraocular melanoma.[70] These are the main outcomes that differ between PBT and alternative treatments (plaque brachytherapy or enucleation).

Head and neck QoL

Non-comparative studies of PBT showed that QoL did not deteriorate during PBT for skull base tumours. PROs were higher for PBT than PRT for head/neck cancer. [67]

C.4. TRANSFORMATION ISSUES

The transformation issues as stated in Table 16 were the following:

Utility weights applied to the economic model

Comparative quality of life data is limited for PBT. In addition, the Paediatric QoL instrument cannot be mapped to the utilities in the paediatric PICO population.

Healthcare resource use and associated costs

These have been discussed in detail in Section C.3.

C.5. ANY OTHER TRANSLATION ISSUES

None.

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

Not applicable.

SECTION D   ECONOMIC EVALUATION

D.1.   OVERVIEW

Although the PICO Confirmation stated that the required economic analysis was either a cost-utility or a cost-effectiveness analysis, a cost consequences approach was used for the following reasons:

- A disaggregated approach was employed because the benefit and cost evidence available could not be combined into a single indicator of a net benefit, or one off net cost. This Assessment Report presents an array of health outcome measures alongside costs.
- Comparative information on all the PICO populations is lacking. There is limited evidence in paediatric, head and neck and ocular melanoma, and scarce comparative evidence in the other populations. There are gaps in the evidence so that combined measures across populations of comparative evidence of IMRT to PBT could not be developed.
- A review of the literature on cost-effectiveness evaluations of PBT and the consensus of three reviews of the cost-effectiveness analyses presented below, lead to the opinion that modelling efforts were not compelling. The modelling methodology was appropriate in the studies, but the results were dependent on strong assumptions needed to deal with the lack of good evidence. This Assessment Report could not improve on existing models in terms of providing appropriate evidenced-based parameters for a model.
- The various benefits of treatment are measured in different units, and are fundamentally different from one another, therefore they cannot be measured in a common unit of benefit. This Assessment Report does not try to conform to the ICER approach that requires measuring all of the costs and benefits in money terms. A clear and transparent presentation of a wide array of costs and benefits contribute to an informed discussion and decision.
- The clinical evaluation suggested that, relative to the comparator, the intervention has uncertain safety and uncertain effectiveness based on the evidence profile given in Section C.

Table 23 describes the framework that was used to classify the clinical evidence in Section B so that a decision could be made about the type of economic analysis to undertake in this Section.

Table 23   Classification of the comparative effectiveness and safety of the proposed therapeutic medical service compared with its main comparator and guide to the suitable type of economic evaluation

Comparative safety	Comparative effectiveness			
	Inferior	**Uncertain[a]**	**Non-inferior[b]**	**Superior**
Inferior				
Uncertain[a]		PBT versus PRT, plaque brachytherapy Cost consequences		
Non-inferior[b]				
Superior				

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

Notes: 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 'non-inferiority' is the preferred basis for demonstrating equivalence

D.1 POPULATIONS AND SETTINGS

In the 2017 HealthPACT Report, the demand for particle therapy is estimated. They used 2009 Australian cancer incidence data, obtained from the Australian Cancer Database, adjusted to the 2014 population. They also used Australian recommendations on optimal radiotherapy utilisation rates, [50] and from this assumed eligibility rates for particle therapy substitution. Particle therapy uses particles (protons or carbon ions) instead of photons. Potential demand was calculated for nine malignancy indications (see Table 17) and those included in the PICO are reported in Table 19. The report states that "This approach estimated that the total number of patients who would be potentially eligible for particle therapy is estimated to be 3,878 persons, including 203 paediatric patients. At the time, this patient number was considered by the Australian New Zealand Society of Nuclear Medicine (ANZSNM) as a very high end estimate, due to the challenges of calculating particle therapy eligibility rates, which would be based on the strength of clinical evidence, patient clinical need, and the caseload capacity of local facilities. However, it was provided as a guide to potential demand, and an indicator for longer term future planning." Note that 55 paediatric patients in 2014 were considered candidates for PBT and not PRT, reported as a negative difference. This number increases to 58 in 2017 estimation. This approach has been adopted in this Assessment Report for the analysis. Table 24 presents the PICO patients eligible for PRT and PBT for 2014 and 2017, being adjusted for population growth.

Table 24   Estimation of Australian patients eligible for particle therapy 2017 in PICO population

Cancer	Conventional radiotherapy (PRT)		PBT[b]		Difference between PRT & PBT	
Year	2014	2017[a]	2014	2017[a]	2014	2017[a]
Brain/CNS	1,308	1,377	599	631	709	747
Head and neck/skull	1,919	2,021	900	948	1,019	1,073
Ocular	248	261	167	176	81	85
Paediatric Medulloblastoma	148 (116)	156	203	214 (116)	-55	-58
TOTAL	3,623	3,815	1,869	1,968	1,754	1,847

Source: HealthPACT 2017 Report [6]
Abbreviations: PRT, photon radiation therapy; PBT, proton beam therapy; CNS, central nervous system
Notes:
a Population growth between 2014 and 2017 was estimated to be 5.3% from ABS Online (accessed October 2017)
b This Report assumes that all candidates eligible for particle therapy (PBT and carbon ion therapy) are treated with PBT.

D.2 STRUCTURE AND RATIONALE OF THE ECONOMIC EVALUATION

A summary of the key characteristics of the economic evaluation is given in Table 25.

Table 25   Summary of the economic evaluation

Perspective	Societal / payer
Comparator	PRT, Plaque brachytherapy, IMRT, palliative care
Type of economic evaluation	Cost consequences
Sources of evidence	Cost-effectiveness analyses, Systematic review
Time horizon	Treatment period / years of follow-up from treatment
Outcomes	No difference in disease-free and overall survival and disease-related and all-cause mortality No difference in health-related quality of life Tumour regression and remission rates Incidence of metastases Difference in AEs
Methods used to generate results	Reference to the published literature
Discount rate	N/A
Software packages used	N/A

Abbreviations: PRT, photon radiation therapy; IMRT, intensity modulated radiation therapy

Table 26 summarises the cost-effectiveness literature on PBT applicable to the PICO population, as well as other factors such as changes to Intelligence Quotient (IQ) and QoL.

Table 26   **Review of Economic Evaluations**

Study	Intervention	Comparator	ICER	Study conclusion
Paediatrics				
Lundvist 2005[2], Sweden (2002 costs), Medulloblastoma	PBT	IMRT	-€23,600/QALY	PBT superior in children aged 5 years due to less IQ loss, hearing loss, and GHD; however the same utility values were used for paediatric and adult life; QoL secondary to IQ and hearing loss not considered
Mailhot-Vega 2013, US (2012 costs), Medulloblastoma	PBT	IMRT	PBT US$4,617/QALY; IMRT US$8,108/QALY	PBT superior in children aged 5 years owing to reduction in adverse effects; however did not consider QoL
Hirano, 2014, Japan (2012 costs), Medulloblastoma	PBT	IMRT	$11,773 USD/QALY or $21,719 USD/QALY (depending on QoL scale used)	PBT may be cost-effective in children aged 6 years; however, IQ and lifetime productivity/wage loss were not considered, operational costs may not have been appropriate, and there was high variability in sensitivity analysis
Head and Neck				
Lundkvist 2005[1], Sweden (2002 costs)	PBT	PRT	US$4,254/QALY	PBT potentially cost-effective in patients aged 65 years with head and neck cancer compared to PRT; interpret with caution due to lack of long-term toxicity and QoL data
Raemakers, 2013, Holland (2010 costs)	PBT (IMPT)	IMRT	Mixed vs IMRT, €60,278/QALY; IMPT vs mixed, €127,946 /QALY;	PBT was associated with increased costs at all examined levels and does not appear to be cost-effective versus IMRT
Ocular Melanoma				
Moriarty	PBT	Enucleation Plaque Brachy therapy	Enucleation ICER: US$106,100/QALY	Results were highly sensitive to multiple parameters. All three treatments were considered optimal, and even dominant, depending on the values used for sensitive parameters

Abbreviations: GHD, growth hormone deficiency; PBT, proton beam therapy; PRT, photon radiation therapy; IMRT, intensity modulated radiation therapy; IMPT, intensity modulated proton therapy; IQ, intelligence quotient; QALY, quality adjusted life year; QoL, quality of life; USD, United States dollar

Cost-effectiveness analysis in the paediatric population

The lengthy side-effect profile associated with craniospinal PRT renders paediatric medulloblastoma an attractive malignancy for the use of PBT. The use of PBT may prevent lifelong chronic diseases through the avoidance of irradiating a large volume of normal tissue and by sparing a substantial

amount of brain from receiving higher doses of radiation. This assertion has been made repeatedly by clinicians and arises from the perceived technological superiority in precision in hard to treat tumours.[71] The data supporting the assertion has not accrued to date.

A study by Lundkvist et al (2005) assessed the cost-effectiveness of PBT compared with conventional radiation therapy in the treatment of childhood medulloblastoma.[54] The base case results showed that PBT was associated with €23,600 in cost savings and 0.68 additional QALYs per patient. The analyses showed that reductions in IQ loss and GHD contributed to the greatest part of the cost savings and were the most important parameters for cost-effectiveness. The consequences of radiation therapy were evaluated using a Markov simulation model. Children, aged five years with medulloblastoma, were followed. The patients were at risk of several types of AEs, including hearing loss, IQ loss, hypothyroidism, GHD, osteoporosis, cardiac disease, and secondary malignancies. The patients were also at risk of death and were divided into risk groups for normal death: death due to tumour recurrence, treatment-related cardiac death, treatment-related subsequent tumour death, or treatment-related to other death. A review of the literature was conducted to estimate the parameters in the model. The structure of the model used was valid, however a number of assumptions were necessary to obtain the results reported as presented in Table 27.

Table 27   Assumptions made in the economic model by Lundkvist et al 2005

Number	Assumption
1	A yearly mortality risk of 8% during the first 10 years in the base case.
2	A yearly risk of 0.6% for death due to recurrence of the medulloblastoma was assumed.
3	The radiation-induced deaths appeared 10–20 years after primary diagnosis and treatment. and children who have medulloblastoma have a lower risk of developing secondary malignancies compared with children who have other types of primary malignancies.
4	Assumptions with lower risks of hearing loss also were tested, because the risk of hearing loss is related highly to the radiation dose to the inner ear and, thus, to the beam arrangement; thus, the risk of hearing loss may vary substantially between patients.
5	The extent to which IQ loss can be attributed to radiation or whether the risk of IQ loss is lower when using proton radiation remains unknown. In the base case analysis, it was assumed that 25% of the IQ loss was related to radiation therapy.
6	Assumed that all episodes of hypothyroidism occurred 4 years after the primary diagnosis.
7	The risk of nonfatal secondary malignancies, like the risk of fatal secondary malignancies, is somewhat uncertain; therefore, different assumptions were tested in the sensitivity analyses.
8	It is plausible that many patients will have several AEs, but is not certain that the costs of the individual AEs will be additive in patients who have multiple events.
9	Mortality was not assumed to incur any costs, only reductions in life years and QALYs.
10	Only 25% of the patients with radiation-induced hearing loss would incur cost; it was assumed that the remaining 75% of patients would not incur a cost.
11	It is plausible that children with IQ loss will incur substantial costs during childhood and adolescence due to increased needs for personal assistants, special school training, etc.; however, no data on these increased needs were available.
12	The cost of GHD was based on the assumption that all children need growth hormone substitute up to age 19 years and that 10% of patients will need life-long substitution.
13	The yearly cost for osteoporosis was estimated based on results from a previously developed simulation model of osteoporosis.

Number	Assumption
14	Osteoporosis would become symptomatic at age 20 years and would continue until death.
15	Patients who had different types of side effects would have a percentage reduction in utility.
16	Only 25% of patients would have severe radiation-induced hearing loss leading to the assumed utility reduction (i.e., the same patients who also incurred the higher costs due to their hearing loss).
17	In the base case, assumed relative mortality risks of 0.05 for treatment-related cardiac death and 0.6 for other deaths and secondary malignancies in patients who were receiving proton radiation compared with conventional radiation.

Source: Lundkvist et al 2005[54]
Abbreviations: IQ, intelligence quotient; QALYs, quality adjusted life years; GHD, growth hormone deficiency.

The high cost of GHD had a strong effect on the results of the study. This was due to the cost of GHD treatment exceeding the cost of PBT, and it was assumed that PBT would reduce the need for continued long-term GHD therapy. There was also a corresponding decrease in QoL associated with GHD.

The structure of the Lundkvist model in terms of transitional probabilities is similar to the structure of the models following it, like the Moriarty and Ramaekers models reported below.

An interesting, and useful, contribution to understanding the economics of treatment with PBT was made in the Lundkvist analysis. They estimate the risk reduction with PBT. They "assumed relative mortality risks of 0.05 for treatment-related cardiac death and 0.6 for other deaths and secondary malignancies in patients who were receiving proton radiation compared with conventional radiation. The relative risks of hearing loss, hypothyroidism, GHD, IQ loss, and osteoporosis all were estimated at 0.12 based on a study by Miralbell et al."[72] These estimates used in their base case generate the cost and dis-utility of AEs avoided and subsequent analyses. Table 28 summarises the analysis. Note, these estimates were based on an analysis conducted in 2002 and technological improvements in therapy have occurred since then.

Table 28   Radiation-Induced Events per 100 Patients Childhood medullablastoma

Variable	Hearing loss	Hypothyroidism	Osteoporosis	GHD	Nonfatal secondary malignancies	Fatal events
Conventional radiation	11.9	16.3	0.4	17.1	1.2	1.91
Proton radiation	1.4	2.7	0.1	2.0	0.7	0.38
Difference	10.5	13.6	0.3	15.1	0.5	1.53

Source: Lundkvist et al 2005[54]
Abbreviations: GHD, growth hormone deficiency

Mailhot-Vega (2012) evaluated consequences of radiation therapy in children with medulloblastoma using a Markov cohort-simulation model-based upon the model by Lundkvist reviewed above.[58] US costing data included the cost of investment and the costs of diagnosis and management of adverse health states from institutional and Medicare data. Longitudinal outcomes data and the Lundkvist model informed risk parameters for the model. ICERs were used to measure outcomes. A cost per hour per room was obtained, assuming a 10-hour treatment day and a 40-year facility lifespan,

excluding holidays and weekends. According to Packer et al[73], 31 fractions were expected, including 13 fractions of 60-minute cerebrospinal irradiation and 18 fractions of 20-minute posterior fossa boost. The cost per room per hour multiplied by 19 hours of room use represented the cost for the operational and capital costs to manage one patient with paediatric medulloblastoma in 2012. Results from the base case demonstrated that PBT was associated with higher QALYs and lower costs; therefore, it dominated PRT. Probabilistic sensitivity analysis illustrated the domination of PBT over PRT in 96.4% of simulations.

A study by Hirano evaluated the cost-effectiveness of PBT with cochlear dose reduction compared with conventional PRT for medulloblastoma in children six years of age.[74] A Markov model and three types of QoL measures were used for estimation of QALYs. The ICER for PBT compared with PRT was calculated for each HRQoL. Sensitivity analyses were performed to model uncertainty in these parameters. The results were sensitive to discount rate, the risk of hearing loss after PBT, and costs of proton irradiation. Cost-effectiveness acceptability curve analysis revealed a 99% probability of PBT being cost-effective at a societal willingness-to-pay value. PBT with cochlear dose reduction improves health outcomes at a cost that is within the acceptable cost-effectiveness range from the payer's standpoint.[75] The model was based on significant assumptions, with extrapolation of outcomes highly uncertain. Cochlear doses were calculated using treatment plans for just eight patients. The wide disparity in the cost of the respective therapies ¥26,943 for PBT and ¥3,082 for IMRT (Japanese Yen) used has to be questioned.

Cost-effectiveness analysis of head and neck

A study done in Sweden by Lundkvist, used a Markov model similar to the one used in another publication reported above on paediatric tumours.[76] Head and neck cancers were evaluated along with cancers not covered in the PICO. The results showed the cost of PBT was just €3,887 higher per patient, with a relatively large 1.02 QALYs gained from PBT when including modelled long-term AEs and assumptions about mortality, QoL and utilities. The model results indicate that the cost-effectiveness of PBT for head and neck cancer could be substantial, although the lack of toxicity data for PBT in head/neck cancers at the time of publication renders its applicability questionable. The results of the model were substantially dependent on the assumptions used on the long-term outcomes from AEs due to IMRT.

Ramaekers et al (2013) used a Markov model in The Netherlands for patients with stage III and IV oral cavity, laryngeal, and pharyngeal cancers.[77] Cohorts were divided into three groups: IMRT for all patients, IMPT for all patients, and mixed IMPT/IMRT with IMPT only if it was "expected to be cost-effective" (which was calculated based on the estimated 6-month risk of xerostomia). Radiation Therapy Oncology Group (RTOG) grades of normal tissue complications were specifically used to define toxicities. At 12 months, xerostomia and dysphagia rates were 22% and 18%, respectively, with IMPT; 36% and 21%, respectively, with mixed IMPT/IMRT; and 44% and 23%, respectively with IMRT. Although all three groups had similar gains in QALYs (IMRT, 6.52; IMPT, 6.62; mixed IMPT/IMRT, 6.56),

costs were €50,989 for IMPT, €41,038 for IMRT and €43,650 for mixed IMPT/IMRT. This is the strongest evidence to date suggesting that select patients with head/neck cancer may have decreased side effects during treatment with nearly the same RT costs as standard of care IMRT. However, the lack of clinical data continues to hamper interpretations from this study. Utility scores were based on a poorly performed cross-sectional analysis, and probabilities of disease progression were also based on outdated studies. Nevertheless, despite incomplete characterisation of toxicities (e.g. need for gastrostomy tubes), this report remains the only study to date that has demonstrated a cost-effectiveness benefit from PBT in head/neck cancers. Therefore, further characterising the population of patients with head/neck cancer who can benefit most from PBT is of great clinical interest not only for future toxicity analyses but also for CE analyses.

The Raemakers study uses a model to predict comparative difference in AEs from treatment with PBT and PRT. There have been some improvements on this model and this is reported in Table 29.[56] This model can be used to generate the number of toxicities averted by the use of PBT in Australia.

Cost-effectiveness analysis of ocular melanoma

Moriarty et al, constructed a Markov model for treatment options: enucleation, plaque brachytherapy, and PBT.[70] Five distinct health states were considered: post-treatment, local recurrence, metastatic cancer, death due to disease, and death due to other causes. The analyses consisted of a hypothetical cohort and a time horizon of the model was five years, and each model cycle represented one year. Model parameters were identified from the published literature and publicly available data sources. Cost-effectiveness of each treatment was calculated in 2011 USD per QALY. ICERs were calculated assuming enucleation as reference. One-way sensitivity analyses were conducted on all model parameters. Enucleation had the lowest costs and QALYs, and plaque brachytherapy had the highest costs and QALYs. Compared with enucleation, the base case ICERs for PBT was US$106,100/QALY. Again, the results were highly sensitive to 13 of 18 parameters used in the model. All three treatments were considered optimal, and even dominant, depending on the values used for sensitivity parameters.

Systematic reviews of cost-effectiveness analysis

In "A Systematic Review of the Cost and Cost-Effectiveness Studies of Proton Radiotherapy" Verma, et al (2016) conclude that "With greatly limited amounts of data, PBT offers promising cost-effectiveness for pediatric brain tumors, well-selected breast cancers, loco-regionally advanced NSCLC (Non-Small Cell Lung Cancer), and high risk head/neck cancers.[48] Heretofore, it has not been demonstrated that PBT is cost-effective for prostate cancer or early stage NSCLC. Careful patient selection is absolutely critical to assess cost-effectiveness. Together with increasing PBT availability, clinical trial evidence, and ongoing major technological improvements, cost-effectiveness data and conclusions from this analysis could change rapidly."

In a Canadian Agency for Drugs and Technologies in Health (CADTH) report they cite the Verma summary and concur with the summary of cost-effectiveness assessments. "Most evidence supported cost-effectiveness in pediatric brain tumors... Under some circumstances cost-effectiveness was demonstrated in high-risk head and neck cancers,[58] but these results were mostly borderline and dependent on unreliable assumptions. The review authors noted that emerging clinical evidence and cost reductions owing to improved technology would likely affect these conclusions. Further, variation in the approach to these analyses and perspectives assumed, as well as the patient populations assessed greatly limits the generalisability. Results should be interpreted accordingly."[46]

The CADTH report noted that the Lundquist study in head and neck tumours PBT was "'considered cost-effective compared to PRT; however, this analysis did not consider long-term toxicity." Conversely, they reported on the Raemeakers Dutch study that PBT was not cost-effective versus IMRT in head and neck cancers.[46]

The CADTH report on cost-effectiveness in paediatric cancers stated that "In patients with medulloblastoma, it was reported by four economic evaluations from the Swedish, American, and Japanese perspectives that treatment with PBT was cost-effective.[54, 58, 74, 76] However, it should be noted that there were issues with the evaluations. This included extrapolation of adult utility values to the paediatric population; assumption of reduced IQ loss, hearing loss and growth hormone deficiency with PBT use; lack of data for quality of life effects secondary to IQ and hearing loss; identical costs for growth hormone in adults and children; incomplete estimation of operational costs; and lack of accounting for productivity losses. One study in patients with brain tumours reported that PBT was considered cost-effective over a broad range of costs."[47].

Washington State HTA reviewed cost-effectiveness analyses and concluded that although the results were reviewed in terms of incremental cost-effectiveness. They pointed out each assumption needed and where evidence was lacking. The evidence should be viewed relative to their review of the outcomes measured and the relatively poor level of evidence quality. They note that the economic evaluations could be improved as better evidence is made available.

In conclusion, the models employed in the economic literature were appropriately constructed in order to evaluate the incremental cost-effectiveness of PBT. However, they either employed poor quality evidence as inputs, or employed strong assumptions (approximations) to make up for the lack of comparative evidence. This Assessment Report did not attempt to adopt a recursive (repetitive) decision tree model or any other type of simulation. It is not a matter of proper model specifications, but lack of evidence that precludes the use of such models in the evaluation of PBT. In the discussion of his model Moriarty states that "In our model, we find that PBT can be cost-effective, dominant, or not cost-effective depending on the parameter estimates. This further highlights the lack of empirical comparative evidence for proton beam therapy that has been highlighted in previous systematic reviews."[70] [70]

Markov chains provide support for problems involving decision on uncertainties through a continuous period of time, when cohorts of patients are assumed to move from one health state to another. They can be used for economic evaluation in health care taking into account the evaluation of costs and clinical outcomes, especially for evaluation of the progression of chronic diseases, like hypertension and diabetes. There is not a clear need to model outcomes in a probabilistic manner via a Markov model when working with the small numbers of the PICO cancer populations. The accuracy and applicability of a Markov approach needs to be questioned.

Costing in economic evaluations

Table 29 includes comparisons of cost information on PBT and IMRT. Some reports on cost explicitly stated that the cost estimates were "operating costs", with various descriptions such as running costs or treatment only costs. Thaker simply stated a ratio of 2.8 of PBT/IMRT operating costs.[78] Some evidence was reported as average treatment cost, and it was assumed that some sort of allocation of capital costs was made in the estimate. Some cost-effectiveness studies did not report the individual average per patient costs of treatment, so they could not be included. Studies on prostate cancer were included because the reporting on cost was explicit. The source is reported when it was available from the studies. US Medicare pays about $19,000 for a full dose of standard radiation therapy, but it pays $32,000 for PBT in 2017 Medicare procedures schedule.[79]

Table 29 also includes a ratio of operating costs per patient, and average total cost per patient in order to show comparison between those indices. Such a ratio can help when making comparisons across institutional settings, countries, and time. The range of the ratios of PBT/IMRT operating cost was 1.43 to 3.44, and for the studies reporting average total cost 1.21 to 2.26. The ratio from the Hirano study being an outlier at over 8. In the Raemakers evaluation, they simply assumed that PBT would be twice as costly as IMRT.[77] The cost reflects higher charges for PBT.

Table 29   Operating and average costs per patient for PBT and IMRT from the economic literature

Study	Operating cost (various currency)			Average total cost (various currency)			Source/Currency	Tumour	Year study published
	PBT	IMRT	Ratio	PBT	IMRT	Ratio			
Moriarty[70]	12,438	8,678	1.43				USA National Inpatient Survey; Medicare fees	Intraocular melanoma	2011
Lundkvist[54]	10,218	4,239	2.41				Euros	Childhood medulloblastoma	2002
Hirano[74]				26,943	3,082	8.74	Japanese medical service fees	Childhood medulloblastoma	2012
Base case*	29,693	11,877	2.5				Australian dollars	PICO groups	
Mailhot Vega[58]				69,412	33,068	2.1	US dollars Medicare fees	Breast	2012
Peeters[59]	39,610	11,500	3.44				Euro, Activity based costing: literature, clinic, Vanderstraeten[60]	Head and neck	2010
Raemakers[77]	20,076	10,036					Euros, activity based	Head and neck	2013
Lundkvist[76]	14,700	7,600	1.93				Euros	Multiple	2005
Thaker[78]			2.80				US dollars Medicare fees	Multiple	2015
Vanderstraeten[60]	28,296						Euro, Activity based costing public; Belgium	Multiple	2013
Goitien[66]	14,700	7,600	1.93				Euro	Cost analysis	2003
Grutters[80]				27,567	22,696	1.21	Euros	NSCLC	2007
Ollendorf[45]				53,828	37,861	1.42	US dollars Medicare fees	Prostate	2009
Parthan[81]				65,250	28,805	2.26	US dollars	Prostate	2012

Abbreviations: PBT, proton beam therapy; IMRT, intensity modulated radiation therapy.
Notes: *Base case is treatment with 33 fractions at 2.5 times the current MBS fee schedule rate for photon treatment, without anaesthesia.

D.3 VARIABLES IN THE ECONOMIC EVALUATION

MEDICAL DIRECT COSTS

The "base case" cost of PRT in childhood medulloblastoma, ocular, and head in neck has been derived from the Australian MBS 2017 fee schedule using 33 visits at a treatment charge of $182.90 (item# 1555), 33 visits at a treatment verification charge of $76.60 (item# 15715), and a dosimetry plan charge of $3,313.85 (item# 15565). The median number of 33 visits was taken from Johnstone's analysis.[64] The protocols of ongoing clinical trials in ocular and head and neck cancer called for the patients to be treated five days per week for six to eight weeks. The cost of PRT in terms of MBS fees for treatment multiplied by the rate for each treatment is used to obtain the cost of PRT treatment. We assumed that the number of treatment sessions for PBT were the same as that of PRT. The protocols of ongoing clinical trials that specify the treatment regimens were used to check this assumption.[82-84] A recent RCT for dosimetric purposes had 36 visits for paediatric medulloblastoma.[73]

The assumptions used in our base case were that:

A) PBT service has 2.5 times the current MBS fees for PRT
B) PBT and PRT has the same number of fractions per treatment course
C) other charges such as gastric tubes would also be similar across therapies
D) anaesthesia is used for all paediatric PBT treatments (as is the case for current PRT treatments)

Table 30   MBS Item Numbers and Descriptions of current PRT

MBS Item	MBS Description	Scheduled Fee
15275	RADIATION ONCOLOGY TREATMENT with IGRT imaging facilities undertaken: (a) To implement an IMRT dosimetry plan prepared in accordance with item 15565; and (b) utilising an intensity modulated treatment delivery mode (delivered by a fixed or dynamic gantry linear accelerator or by a helical non C-arm based linear accelerator), once only at each attendance at which treatment is given.	$182.90
15565	Preparation of an IMRT DOSIMETRY PLAN, which uses one or more CT image volume datasets, if: (a) in preparing the IMRT dosimetry plan: (i) the differential between target dose and normal tissue dose is maximised, based on a review and assessment by a radiation oncologist; and (ii) all gross tumour targets, clinical targets, planning targets and organs at risk are rendered as volumes as defined in the prescription; and (iii) organs at risk are nominated as planning dose goals or constraints and the prescription specifies the organs at risk as dose goals or constraints; and (iv) dose calculations and dose volume histograms are generated in an inverse planned process, using a specialised calculation algorithm, with prescription and plan details approved and recorded in the plan; and (v) a CT image volume dataset is used for the relevant region to be planned and treated; and (vi) the CT images are suitable for the generation of quality digitally reconstructed radiographic images; and (b) the final IMRT dosimetry plan is validated by the radiation therapist and the medical physicist, using robust quality assurance processes that include: (i) determination of the accuracy of the dose fluence delivered by the multi-leaf collimator and gantry position (static or dynamic); and (ii) ensuring that the plan is deliverable, data transfer is acceptable and validation checks are completed on a linear accelerator; and (iii) validating the accuracy of the derived IMRT dosimetry plan in a known dosimetric phantom; (iv) determining the accuracy of planned doses in comparison to delivered doses to designated points within the phantom or dosimetry device; and (c) The final IMRT dosimetry plan is approved by the radiation oncologist prior to delivery.	$3,313.85

MBS Item	MBS Description	Scheduled Fee
15715	RADIATION ONCOLOGY TREATMENT VERIFICATION of planar or volumetric IGRT for IMRT, involving the use of at least 2 planar image views or projections or 1 volumetric image set to facilitate a 3-dimensional adjustment to radiation treatment field positioning, if: (a) the treatment technique is classified as IMRT; and (b) the margins applied to volumes (clinical target volume or planning target volume) are tailored or reduced to minimise treatment related exposure of healthy or normal tissues; and (c) the decisions made using acquired images are based on action algorithms and are given effect immediately prior to or during treatment delivery by qualified and trained staff considering complex competing factors and using software driven modelling programs; and (d) the radiation treatment field positioning requires accuracy levels of less than 5mm (curative cases) or up to 10mm (palliative cases) to ensure accurate dose delivery to the target; and (e) the image decisions and actions are documented in the patient's record; and (f) the radiation oncologist is responsible for supervising the process, including specifying the type and frequency of imaging, tolerance and action levels to be incorporated in the process, reviewing the trend analysis and any reports and relevant images during the treatment course and specifying action protocols as required; and (g) when treatment adjustments are inadequate to satisfy treatment protocol requirements, replanning is required; and (h) the imaging infrastructure (hardware and software) is linked to the treatment unit and networked to an image database, enabling both on line and off line reviews.	$76.60

Abbreviations: PBT, proton beam therapy; IMRT, intensity modulated radiation therapy; IGRT, image guided radiation therapy; CT, computed tomography.

PATIENT COSTS

The cost of transportation and hotel accommodation should be considered, since a majority of the patients treated at a national PBT facility would be living away from the facility and require travel and accommodation. Transportation costs for PRT would be much less, since there are 197 LINACs in 76 facilities in Australia.

HOSPITALISATION COSTS

Some patients in some tumour groups, especially within the paediatric tumour group, will require hospitalisation. This does not appear to be determined by type of treatment, PRT or PBT. Plaque brachytherapy does require hospitalisation, so is an additional cost of that treatment in ocular cancers.

ADVERSE EVENTS

The number of AEs expected from the use of PRT to PBT for the population expected to be candidates for PBT in Australia are obtained from methods used to estimate events in the literature.[54, 70].

Cost of adverse events

Medical direct treatment cost values are identified for those events that are covered by Medicare. Other costs of care for AEs are noted but not quantified, such as dental costs or speech therapy costs.

D.4 RESULTS OF THE ECONOMIC EVALUATION

The results are presented in two formats below. The first is a listing of information on the costs and consequences of PBT in the PICO populations. The second is an estimate of the medical direct cost of

treating the population eligible for treatment with PBT as a whole, and the subset of PICO population eligible for treatment.

COST AND CONSEQUENCES

The cost and consequences are broken down and reported for three populations: Paediatric, Ocular, and Brain/Spinal. This follows the evaluation of the clinical outcomes and harms in Section B and also the evaluation by the Washington Technology Assessment Group, where it lists ocular and paediatric cancers as having moderate evidence on benefit and harms, and the brain/spinal area having limited information but important reduction in harm reported for PBT.

Below are comments on the cost and consequences of PBT as compared to conventional therapy comparison in these areas:

Paediatric

The expected number of paediatric cancers to be treated with PBT is 214 per year in 2017, with 158 of these patients also being candidates for treatment with conventional therapy (refer to Table 24).

- There is an increase in the cost born by the family of the patients treated by PBT in terms of transportation costs and accommodation (and hospitalisation) incurred during six weeks of therapy. This assumes that most Australians would not be living in close proximity to a PBT facility. This assumption is realistic given the high capital costs of building a facility.
- In non-comparative studies of QoL in paediatric patients (before and after PBT), demonstrated improvements in QoL during therapy, with additional increases thereafter.
- In 2017, there are an estimated 58 children who are candidates for treatment with PBT but not with PRT.[45] For this group, PBT therapy would add benefit proportional to the progression free survival rate from PRT. This would be a net gain to the health of the population of paediatric cancer patients, to be set against the cost of providing PBT treatment facilities in Australia. Presently, some of these benefits are afforded to the patients of the MTO Program. The estimated medical direct cost for these fifty-eight patients is $1,909,788 per year, assuming that PBT is priced 2.5 times higher than PRT (includes anaesthetic for each treatment fraction).
- Focusing on just childhood medulloblastoma, the HealthPACT study reported that 116 paediatric patients in Australia were candidates for brain tumour treatment in 2014 to estimate the AEs. Using the methodology from Lundkvist for estimating radiation-induced events per 100 patients, would lead to the following yearly AE estimates which could be reduced by the use of PBT rather than conventional PRT for childhood medulloblastoma.

Table 31   Radiation-induced adverse events averted by PBT in childhood medulloblastoma

	Hearing loss	Hypothyroidism	Osteoporosis	GHD	Secondary malignancies	Fatal events
No. of patients with radiation-induced events averted by PBT vs conventional RT in childhood meduloblastoma	11.6	15	.33	16.61	.55	1.65

Abbreviations: PBT, proton beam therapy; RT radiation therapy; GHD, growth hormone deficiency

- o If it was assumed that the total population (116) were treated with PBT rather than PRT, then a decrease would be expected in the amount spent to treat hearing loss and a decrease in the amount spent on treating GHD, with many patients needing to be treated long-term for GHD. Both of these outcomes would lead to a decrease in the social cost of treatment with PBT as compared to PRT. There is also evidence that math scores, indicating cognitive ability, are higher with those patients treated with PBT.[85]

- o There is a cost of anaesthesia for young children for both conventional radiotherapy and PBT, though the length of sedation required for PBT may be longer due to longer treatment times. According to the MBS Fee Schedule for anaesthesia for radiotherapy (item 21980), the fee is $99.00. If this fee is charged for each of the 33 visits in the base case, then it would add $3,267 to the cost of conventional radiotherapy and PBT. For the PBT base case of 33 visits, the medical direct costs for treatment of paediatric patients including just radiation costs ($29,693) and anaesthesia costs ($3,267) would be a total of $32,960 per patient.

- o If all 116 patients were treated with PBT in Australia at $32,960 per patient, the scheduled fees set 2.5 higher than PRT fees, it would total $3,823,404. This cost would be offset by a decrease in the cost of treating GHD, less cost of treating hearing loss, and hypothyroidism. The benefit would include the avoidance of 1.65 fatal events per year.

Ocular

- Treatment options for patients with ocular melanoma include 1) enucleation, 2) suturing of a radioactive plaque to the eye overlying the melanoma, and 3) PBT. Advantages of the radioactive plaque and PBT are preservation of the eye and vision. PBT has a number of alleged advantages over radioactive plaques, including 1) localisation requires one or no surgery, depending on technique, 2) no hospital stay is needed, yet treatment is still completed in five calendar days, 3) more patients are eligible for PBT than radioactive plaque therapy because of the ability to treat larger tumour sizes and tumours surrounding the optic nerve and 4) medical staff have no radiation exposure.

- Moriarty reported that plaque brachytherapy had the highest cost due to the high cost of hospitalisation in the USA. However, given that hospital costs in the USA are generally in the range of 50% higher than in Australia, the cost difference between PBT and plaque brachytherapy

diminishes.[86] The therapies are roughly similar in cost. Enucleation was 43% less costly than PBT in the analysis.

- Moriarty estimates the following transitional probabilities obtained from systematic review of the literature that illustrates the mixed results in comparative effectiveness over a five year time horizon. The HealthPACT methodology for demand for care in ocular tumours was applied to obtain the number of patients estimated to transition to the health states by therapy. Table 32 presents those estimates.

Table 32   Outcomes probabilities of patients treated for ocular tumours and the estimated annual outcomes in Australia

Outcome	PBT	Plaque brachytherapy	Enucleation
Post-treatment LC probability	0.009	0.021	0.002
Patients per year	1.5	3.5	0.34
Post-treatment metastasis (MT) Probability	0.039	0.029	0.047
Patients per year	6.5	4.8	7.8
LC after MT probability (five year horizon)	0.061	0.045	0.074
Patients per year	0.4	0.21	0.58

Abbreviations: PBT, proton beam therapy; LC, local recurrence; MT, metastasis.

- PBT has less local recurrence than plaque brachytherapy, and more than enucleation. PBT has more metastasis post-treatment than plaque brachytherapy and less than enucleation. Finally, PBT has more long-term local recurrence than plaque brachytherapy and less than enucleation. There is no clear indication that a PBT facility would avert more major morbidity and mortality than the alternative therapies. Enucleation is a therapy with lower medical direct cost but is avoided, unless the ocular function cannot be preserved.

- Protection of vision in the patient is a major concern in ocular cancers. Cataracts, radiation retinopathy, optic neuropathy, and glaucoma can result from plaque brachytherapy. There is conflicting data on whether plaque brachytherapy preserves ocular function better than PBT. Enucleation rates after therapy are also the subject of ongoing debate.

- The cost of episcleral radioactive plaque for choroidal melanomas (MBS#42801) is $1,049.70 for insertion and $524.70 for removal of the beads, includes anaesthetic $99.00 (twice), and ultrasound treatment (items 55008 and 550105) $73.50. The total per patient cost of treatment is $1,836.20.

- The cost of enucleation is $11,043 per patient ((based on DRG CO2Z, DRG weight 2.249, at national efficient price $4,910).[87]

Brain/spinal

- Baseline medical direct cost: Using the MBS fees for PRT gets a basic cost of radiation treatment of $11,877 (assuming 33 visits) but excludes costs for speech therapy, dental care, and treatment

for AEs. Each of these services is provided to patients for PBT and PRT. Treating the 961 patients who were estimated to be treated for head/neck cancer in 2017 would have a total cost of $11,418,417.

- Outcomes: The clinical outcomes of treatment of head and neck tumours are similar with PBT and PRT, except in the proportions of patients having dysphagia, xerostomia, and inflammation of the salivary duct.

- A model-based analysis provides the comparative difference in AEs from treatment with PBT and PRT (see Table 33).[56]

Table 33   Comparative difference in adverse events from treatment with PBT and PRT.

Endpoint	% AEs for PBT	% AEs for PRT	% Difference
Dysphagia ≥grade 2	6.7	15.0	8.3
Dysphagia ≥grade 3	4.9	7.6	2.7
Xerostomia ≥Grade 2	10.0	19.0	9.0
Salivary duct inflammation ≥ grade 2	4.7	7.6	2.9
Feeding tube dependence	1.3	1.7	.4

Source: Rwigema, 2017 #3388
Abbreviations: AEs, adverse events; PBT, proton beam therapy; PRT, conventional photon radiation therapy; ≥ greater than or equal to.
Notes: This table has been modified from the original.

- Cost of treatment of AEs: Using the model-based approach for predicting AEs and the HealthPACT estimates of the demand for PBT in head and neck tumours, the number of AEs averted by using PBT rather than PRT has been estimated (see Table 34).

Table 34   Number of adverse events averted by using PBT rather than IMRT

Endpoint	Number of events averted
Dysphagia ≥grade 2	78.65
Dysphagia ≥grade 3	25.59
Xerostomia ≥Grade 2	85.29
Salivary duct inflammation ≥ grade 2	27.48
Feeding tube dependence	3.79

Abbreviations: PBT, proton beam therapy; IMRT, intensity modulated radiation therapy; ≥, greater than or equal to.

- o Dysphagia grade 2 or higher results in the need for gram sodium fluoride to be used daily and on the average leads to two extra dentist visits.
- o Grade two xerostomia requires the placement and maintenance of feeding tubes and the nutrients used in the feeding.

TOTAL MEDICAL DIRECT COST OF PARTICLE THERAPY AND PBT IN AUSTRALIA

Using the estimates for patients eligible for PBT, it is possible to compute the impact on medical direct cost of introducing PBT to Australia. In Table 17, we have computed the total medical direct cost of treating all the patients eligible for particle therapy using the HealthPACT estimates, extrapolated to

2017, across all indications, before and after introduction of PBT. Total expenditure for all nine indications in this population is $153,677,195 before the introduction of PBT. If only the PICO population (paediatric, head and neck/skull, and ocular) is considered, then the total expenditure in the PICO population is $49,136,604 before the introduction of PBT.

Using the estimates for patients eligible for PBT, it is possible to compute the impact on medical direct cost of introducing PBT to Australia at different cost levels for PBT. The literature on cost and cost-effectiveness of PBT in other countries shows the cost of PBT higher than that of PRT (refer to Table 29). We used a range of 50% to 150% higher cost of PBT relative to PRT in the analysis. The results are presented in Table 35 and Table 36.

This Assessment Report will therefore consider the base case of PBT fees to be 150% higher (or 2.5 times) than current PRT fees.

If it is assumed that all of the patients in the PICO population that are eligible for PBT receive PBT, then the total expenditure on this population on PBT is $58,436,562 for the base case without anaesthetic, or $59,132,433 with anaesthetic. Note that anaesthetic is required when the paediatric is treated with PRT or PBT.

Figure 6 depicts a flow diagram of the number of PICO patients being treated with PRT or PBT in 2017.

Figure 6   Flow diagram of PICO Patients being treated with PRT or PBT in 2017
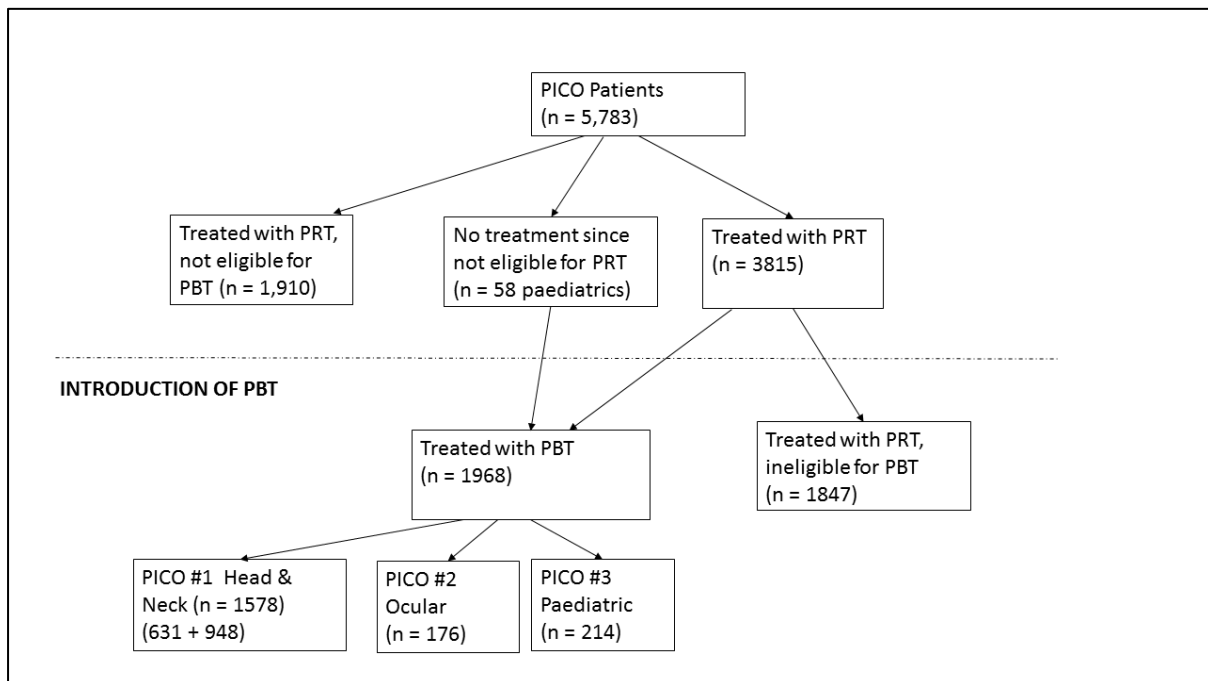
Source: include reference to HealthPACT

Abbreviations: PICO, patient intervention comparator outcomes; PRT, photon radiation therapy; PBT, proton beam therapy.

Table 35 Cost of treatment before and after introduction of PBT for the total population and PICO population in 2017

Patients treated	Treatment Cost/patient	Anaesthetic Cost/patient	Total cost (AU$)
Before Introduction of PBT			
All patients with conventional treatment N = 24,416 (Paediatric n = 156)	$11,877	$3,267*	$290,507,030
Candidates for conventional treatment in the PICO population without PBT N=3,815 (Paediatric n = 156)	$11,877	$3,267*	$45,821,742
After Introduction of PBT for PICO Population			
Eligible for PBT (PBT=2.5x($PRT)) N = 1,968 (Paediatric n = 213)	$29,693	$3,267*	$59,132,433
Not Eligible for PBT, so Will Receive Conventional Treatment N = 1,847 (Paediatric n = 0)	$11,877		$21,937,465
Total expenditures on PICO population			**$81,069,898**

Abbreviations: PBT, proton beam therapy; PICO, patient intervention comparator outcomes
Notes: *Anaesthetic is only required for paediatrics.

We explored three separate percentage mark-ups for PBT. In Table 36, a cost factor of 2.0, 2.5 and 3.0 has been applied to the cost of treatment of PRT for the PBT population. If only the PICO population including paediatric, head and neck/skull, and ocular are considered, and assuming all of those who are eligible for PBT are treated with PBT, then the total expenditure in the PICO population is $47,445,121 with the assumption that PBT is priced at 2.0 times PRT. The cost of treatment in the PICO population rises to $59,132,433 with a cost factor of 2.5, and to $70,819,745 if the cost factor goes to 3.0. The cost of treatment of the PICO population would increase from $69,382,586 to as much as $92,757,211.

Table 36 Cost of PBT with cost factor mark-ups of 2.0x, 2.5x and 3.0x compared to PRT after the introduction of PBT for the PICO population in 2017

Patients Treated	Cost/patient	Anaesthetic/patient	Total Cost (AU$)
Eligible for PBT ((PBT=2.0 ($PRT)) N = 1,968 (Paediatric = 213)	$23,755	$3,267	$47,445,121
Eligible for PBT ((PBT=2.5 ($PRT)) N = 1,968 (Paediatric = 213)	$29,693	$3,267	$59,132,433
Eligible for PBT ((PBT=3.0 ($PRT)) N = 1,968 (Paediatric = 213)	$35,632	$3,267	$70,819,745
Not eligible for PBT, so will receive conventional treatment N = 1,847	$11,877		$21,937,465
Total expenditures on PICO population ($69,382,586 to $92,757,211)			

Abbreviations: PBT, proton beam therapy; PICO, patient intervention comparator outcomes
Notes: *Anaesthetic is only required for paediatrics.

D.5 CONCLUSION

There still 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 ocular and paediatric tumours.

The operating cost associated with PBT is, roughly, 150% to 250% of PRT. In another words, 1.5 to 2.5 times higher than conventional therapy in cost comparisons reported in the literature. None showed equivalent cost relative to PRT. This finding suggests that PBT will need to be priced higher than PRT if cost recovery is to be achieved.

The cost-effectiveness analyses reviewed lack credibility, due to the assumptions used to attempt to compensate for limited data on comparative effectiveness.

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 AEs 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 expected comparative difference in the number of AEs in paediatric medullablastoma between PRT and PBT is very small. The application of a modelled approach to the population eligible for PBT with childhood medullablastoma shows that PBT could lower the incidence of hearing loss by twelve patients, GHD by sixteen patients, hypothyroidism by fifteen patients, and potentially two fatal events. In tumours of head and neck/skull, using PBT will lead to 103 fewer serious cases of dysphagia, eighty-five fewer serious cases of xerostomia, and four fewer cases of dependence on feeding tubes.

The total medical direct yearly expenditure on the PBT eligible PICO population, with a range of PBT MBS fees 150% to 250% of PRT, would cost between $69.4 and $92.8 million. The adoption of PBT has the potential of expanding the expenditure for radiation by $35.5 million should it be priced at 300% of PRT, a reasonable percentage in an international perspective.

The estimate of demand for particle radiation showed that there are an estimated 58 children per year that could potentially benefit from PBT, and they are not candidates for conventional therapy. The number, and prognosis of these patients should be investigated further, and the cost and benefit of PBT treatment should be assessed.

Table 37 summarises the economic evaluation. In the absence of empirical estimates of comparative cost and effectiveness, we can simply indicate the direction and magnitude in comparison.

Table 37   Summary of the economic evaluation comparison between PBT and PRT for the PICO population

Comparison/ category	Comparative Effectiveness	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
Head and neck / skull	Insufficient evidence	PBT >PRT	PBT > PRT +		PBT < PRT

Abbreviations: PBT, proton beam therapy; PRT, photon radiation therapy; PICO, patient intervention comparator outcomes.

SECTION E   FINANCIAL IMPLICATIONS

E.1.   JUSTIFICATION OF THE SELECTION OF SOURCES OF DATA

The estimated demand for PBT for Australia in 2014 was sourced from the HealthPACT ANSTO report (see Table 38).

Table 38   2014 ANSTO estimation of Australian patients eligible for particle therapy for nine indications

Indication	Incidence in 2014		Candidates for conventional radiotherapy in 2014		Candidates for particle therapy[a] in 2014	
	All patients	Paediatric patients	All patients	Paediatric patients	All patients	Paediatric patients
Brain/CNS	1,773	138	1,418	110	709	110
Head and neck/skull	2,609	16	1,931	12	913	13
Ocular	271	23	271	23	190	23
Lung	6,883	2	5,506	2	619	2
Prostate	20,914	0	12,130	0	837	0
Liver	1,402	19	0	0	70	10
Bone	199	43	0	0	100	43
Uterine cervix	830	1	589	1	166	1
Pancreas	2,739	1	1,342	0	274	1
Total	**37,620**	**243**	**23,187**	**148**	**3,878**	**203**

Source: HealthPACT Proton and Heavy Ion Therapy: An Overview January 2017[6]
Abbreviations: ANSTO, Australian Nuclear Science and Technology Organisation; CNS, central nervous system.
Notes: a The ANSTO Report 2014 includes conventional radiotherapy and particle therapy (proton beam therapy or carbon ion therapy). We assume that all particle therapy equates to PBT in this report.

These estimates of demand by indication were used to create Table 39, which is the estimated demand for the tumour areas for the PICO population. The estimates were then extrapolated from 2014 to 2017 with a 5.3% population growth rate from 2014–2017.

Table 39   Estimation of Australian patients eligible for conventional radiotherapy and PBT in 2014 and 2017

PICO no.	Cancer	Conventional radiotherapy		PBT	
	Year	2014	2017	2014	2017
1[b]	Brain/CNS (adult)	1,308	1,377	599	631
	Head and neck/skull (adult)	1,919	2,021	900	948
2	Ocular (adult)	248	261	167	176
3	Paediatric	148	156	203	214
	TOTAL	**3,623**	**3,815**	**1,869**	**1,968**

Source: HealthPACT 2014 Report [6]
Abbreviations: PBT, proton beam therapy; CNS, central nervous system
Notes: a Population growth between 2014 and 2017 was estimated to be 5.3% from ABS Online (accessed October 2017)
b PICO no.1 includes Brain/CNS/Head and Neck/Skull which is larger cohort than listed in the PICO Confirmation, but is the most similar in indications from the available data.

Assuming all patients who could receive PBT were given PBT and that an average of 33 fractions was given for a full course of treatment, we can estimate the number of services for the patient population treated with PBT for the next five years (Table 40).

Table 40   Estimated number of services associated with PBT treatment required annually, extrapolated to 2022

	PBT treatment estimated number of services[a]				
Activity	**2017-18**	**2018-19**	**2019-20**	**2020-2021**	**2021-2022**
Planning services	1,968	1,993	2,018	2,043	2,068
Treatment services	64,946	65,758	66,580	67,412	68,255
Verification services	64,946	65,758	66,580	67,412	68,255
Anaesthesia services[b]	7,054	7,142	7,232	7,322	7,413

Abbreviations: PBT, proton beam therapy.
Notes: a Annual growth is estimated to be 1.25% (reference ABS Online), b Number of services is calculated from number of paediatric patients treated annually multiplied by 33 sessions.

E.2.   USE AND COSTS IN TREATMENT WITH PBT

Since the literature on cost and cost-effectiveness of PBT in other countries shows the cost/fees for PBT is higher than that of PRT (refer to Section D Table 29), this Assessment Report assumes (in the absence of any applied for prices) that the base case will be fees for PBT that are 2.5 times higher than current MBS fees for PRT.

Using this assumption, the estimated costs for PBT services are listed in Table 41.

Table 41   Costs of PBT services[a]

Dosimetry planning (item no. 15565)	Treatment[b] (item no. 15275)	Verification (item no.15715)	Anaesthetic (gas) for paediatrics only (item no. 21980)
1 session: $8,284.63 each	33 sessions: $457.25 each	33 sessions: $191.50 each	33 sessions: $99.00 each

Source: MBS, Medicare Benefits Schedule Online (accessed October 2017)
Abbreviations: PBT, proton beam therapy
Notes:
a assuming costs are 2.5 times higher than PRT
b MBS Treatment Cost is for IGRT which means image guided radiation therapy, being a process in which frequent 2 and 3 dimensional imaging is captured as close as possible to the time of treatment by using x rays and scans (similar to CT scans) before and during radiotherapy treatment, in order to show the size, shape and position of a cancer as well as the surrounding tissues and bones. Each treatment cost for PRT is $182.90.

Table 42 shows the number and costs of PRT services over the next five years for the PICO patients which will be displaced once PBT is introduced.

Table 42   Number and costs of PRT services displaced for PICO patients who will be treated with PBT

Service	2017-18		2018-19		2019-20		2020-21		2021-22	
	Number of activities[a]	Cost of activities	Number of activities	Cost of activities	Number of activities	Cost of activities	Number of activities	Cost of activities	Number of activities	Cost of activities
Planning	1,910	$6,329,642	1,934	$6,408,763	1,958	$6,488,872	1,983	$6,569,983	2,007	$6,652,108
Treatment	63,032	$11,503,318	63,820	$11,647,110	64,618	$11,792,699	65,425	$11,940,107	66,243	$12,089,359
Verification	63,032	$4,828,242	63,820	$4,888,595	64,618	$4,949,703	65,425	$5,011,574	66,243	$5,074,219
Total	**127,974**	**$22,661,203**	**129,573**	**$22,944,468**	**131,193**	**$23,231,274**	**132,833**	**$23,521,665**	**134,493**	**$23,815,685**

Abbreviations: PBT, proton beam therapy; PRT, photon radiation therapy.
Notes:a: These numbers are less than for PBT since there are 58 paediatric patients in 2017 which cannot be treated with PRT.

Table 43 shows the number and costs of PBT services for those PICO patients who are eligible for PBT over the next five years.

Table 43   Numbers and costs of PBT services for PICO patients who are eligible

Service	2017-18		2018-19		2019-20		2020-21		2021-22	
	Number of activities	Cost of activities	Number of activities	Cost of activities	Number of activities	Cost of activities	Number of activities	Cost of activities	Number of activities	Cost of activities
Planning	1,968	$16,304,614	1,993	$16,508,422	2,018	$16,714,777	2,043	$16,923,712	2,068	$17,135,258
Treatment	64,946	$29,631,558	65,758	$30,001,953	66,580	$30,376,977	67,412	$30,756,689	68,255	$31,141,148
Verification	64,946	$12,437,136	65,758	$12,592,600	66,580	$12,750,008	67,412	$12,909,383	68,255	$13,070,750
Total	**131,860**	**$58,373,309**	**133,508**	**$59,102,975**	**136,846**	**$59,841,762**	**140,267**	**$60,589,784**	**143,774**	**$61,347,157**

Abbreviations: PBT, proton beam therapy.

E.3.   CHANGES IN USE AND COST OF OTHER MEDICAL SERVICES

The changes in use and costs calculated in Table 44 are based on the data from Table 28 in Section D.

Table 44   Radiation-Induced Events per 100 patients

Variable	Hearing loss	Hypothyroidism	Osteoporosis	GHD	Nonfatal secondary malignancies	Fatal events
Conventional radiation	11.9	16.3	0.4	17.1	1.2	1.91
PBT	1.4	2.7	0.1	2.0	0.7	0.38
Difference	10.5	13.6	0.3	15.1	0.5	1.53

Source: Lundkvist 2005 [54]
Abbreviations: PBT, proton beam therapy; GHD, growth hormone deficiency

COSTS ASSOCIATED WITH HYPOTHYROIDISM

Hypothyroidism is most commonly treated with the prescription medication, Thyroxine (Oroxine/Eutroxsig/Eltroxin) for the remainder of a patient's life.

Table 45   Estimated Cost for the management/treatment of Hypothyroidism for one patient in 2017

Treatment name	Treatment length	Strength (mg)	PBS item code	DPMQ	Units per pack	Cost per unit	Cost of 14,600 units for typical treatment for 40 years[a]	Cost of typical treatment per year
Prescription medicine, (synthetic thyroxine) (Oroxine/Eutroxsig/Eltroxin)	Long-term	50	2174K	$25.83	200	$0.13	$1,886	$47
		75	9287T	$26.39	200	$0.13	$1,926	$48
		100	2175L	$26.36	200	$0.13	$1,924	$48
		200	2173J	$28.99	200	$0.13	$2,116	$53

Source: PBS Online (accessed October 2017)
Abbreviations: PBS, Pharmaceutical Benefits Scheme; mg, milligram; DPMQ, dispensed price per maximum quantity
Notes:
a Estimated using a patient of 40 years of age, living until 80 years, taking one unit per day.

Assuming that the average cost is $48 per patient annually, for 13.6 patients the total cost is $653 in 2017.

COSTS ASSOCIATED WITH GHD

GHD is an adverse advent of conventional radiation therapy or PBT for medulloblastoma, mostly for the paediatric age group, of which 70% are diagnosed under ten years of age. Furthermore, the majority of paediatric patients will need to be treated for GHD until the age of 19 years of age [54].

Table 46   Estimated Cost for the treatment of GHD for one patient in 2017

Treatment name	Treatment length	Strength (mg)	PBS item code	DPMQ	Units per pack	Cost per unit	Cost of 4,562 units for typical treatment for 12.5 years[a]	Cost of typical treatment per year
Prescription medicine (Somatropin)	Long-term	0.6	10456H	$188.78	7	$26.97	$123,037	$9,843
		4	10447W	$180.12	12	$15.01	$68,476	$5,478
		10	10440L	$439.58	30	$14.65	$66,833	$5,347

Source: PBS Online (accessed October 2017)
Abbreviations: PBS, Pharmaceutical Benefits Scheme; mg, milligram; DPMQ, dispensed price per maximum quantity
Notes:
a Estimated by assuming patient commencing GHD at average age 6.5 years until the age of 19 years, taking one unit per day. Total 4,562 units.

Assuming that the average cost is $5,478 per patient annually, for 15.1 patients the total cost is $82,718 in 2017.

COSTS ASSOCIATED WITH OSTEOPOROSIS

Costs associated with osteoporosis are negligible since Table 44 shows the difference in this AE between PBT and conventional radiation is 0.3 annually.

COSTS ASSOCIATED WITH HEARING LOSS

There are 10.5 more patients suffering hearing loss annually as a result of conventional radiation therapy compared to PBT. The costs associated with hearing loss are not calculated here due to complicated nature of treatment for this condition. Given the low volumes, the aggregate costs would not materially affect the PBT to PRT cost comparison.

COSTS ASSOCIATED WITH SECONDARY MALIGNANCIES

These costs are not calculated here due to complicated nature of treatment for this condition. Given the low volumes, the aggregate costs would not materially affect the PBT to PRT cost comparison.

COSTS ASSOCIATED WITH FATALITIES

These costs are not calculated here due to the complexity of the multiple costs incurred. Given the low volumes, the aggregate costs would not materially affect the PBT to PRT cost comparison.

E.4.   FINANCIAL IMPLICATIONS FOR THE MBS

The financial implications, if public funding was via the MBS, resulting from the proposed listing of PBT are summarised in Table 47. This table shows the costs of PBT offset by the patients who are currently treated with PRT.

Table 47   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; MBS, Medical Benefits Scheme.

E.5.   FINANCIAL IMPLICATIONS FOR GOVERNMENT HEALTH BUDGETS

CAPITAL COSTS

The capital cost of installation of proton beam centres is substantial. It is approximately $41 million per room in a facility, and the facilities are usually one to three rooms. The facilities can be serviceable

for thirty years. Photon radiation machinery is in the range of $5 million for machines that last 5 years. There are seventy-six centres providing PRT in Australia currently. The number treated at a PBT facility might increase as PRT machinery is put out of use, thus increasing the capacity utilisation of the PBT centres. The utilisation rate of a PBT centre affects the efficient use of resources applied to radiation oncology services.

IMPACTS TO THE PBS

There is savings to the Pharmaceutical Benefits Scheme (PBS) with the introduction of PBT (see Table 48) since there are reduced side effects compared to PRT (Table 44). These have been estimated from Table 45 and Table 46.

Table 48   Total savings to the PBS associated with a reduced number of AEs with the introduction of PBT

Adverse events	2017-2018 Cost of medicines	2018-2019 Cost of medicines	2019-2020 Cost of medicines	2020-2021 Cost of medicines	2021-2022 Cost of medicines
Hypothyroidism	$653	$661	$669	$678	$686
GHD	$82,718	$83,752	$84,799	$85,859	$86,932
Sub-total costs	**$83,371**	**$84,413**	**$85,468**	**$86,537**	**$87,618**

Abbreviations: PBT, proton beam therapy; AEs, adverse events; GHD, growth hormone deficiency; PBS, Pharmaceutical Benefits Scheme.

OTHER COMMONWEALTH GOVERNMENT IMPACTS

MTOP and PBT:

Should PBT be made available in Australia, patients clinically assessed as requiring this treatment modality will no longer have access to MTOP funding.

The overall costs to MTOP for financial years 2014/15 and 2015/16 is provided below:

-    2014/15: $<redacted> (<redacted> cases) at an average of $<redacted> per case

-    2015/16: $<redacted> (<redacted> cases) at an average of $<redacted> per case

The costs include medical direct costs, transportation, accommodation, hospitalisation, and cost for an attending physician for a six to eight week course of treatment. The data reflect <redacted> patients per year being sent overseas for PBT. The Assessment team was not provided with details of the outcomes of the treatment, nor the tumour type.

The cost of treatment with PBT depends on the regimen (the number of fractions per treatment) and whether PBT was performed as monotherapy or as multi-modal treatment (i.e. PBT plus adjuvant chemotherapy, or PBT plus surgery).

The prices for procedures and care overseas are negotiated from fee schedules. In many places where there is fee for service payment, the charge to what is actually paid varies by the payer provider arrangements negotiated.

The estimated patient population that could be treated with PBT, as estimated in the HealthPACT methodology, is many times greater than the number of patients transported by the MTO Program. Direct comparisons could not be made.

Many of the costs of treatment would be the same for treatment whether it was given in Australia or overseas. There would be some travel, hospitalisation, and accommodation costs for PBT treatment in Australia, should a single facility be built, as most patients would not be located near the facility. Given the uncertainty, meaningful comparisons between the costs of the MTO Program and the costs of PBT treatment in Australian are not possible.

Section F   Other relevant considerations

F.1.   Health Workforce

Establishment and investment into new PBT infrastructure and treatment services in Australian brings with it considerable impacts on the current health workforce. As there is currently limited clinical expertise in PBT in Australia, there will be a requirement for formal particle radiotherapy training for radiation oncologists, and updated educational programs for local oncology nurses, radiation therapists and radiation oncology medical physicists. Furthermore, the acquisition of accelerator physicists and radiation engineers are also required for PBT.

This section highlights some key issues related to the growth of a new workforce for delivering PBT services to the Australian public and draws upon both developed as well as nascent PBT workforce structures observed internationally.

PBT dosimetry verification'

Currently, Australian PBT patients are required to seek treatment in the United States of America (US) or Europe, where prevailing particle therapy centres and PBT specialised integrated cancer care teams are available.

In the US, PBT was first offered as a treatment modality in 1990 at the Loma Linda University Medical Centre in southern California. As at the beginning of 2017, there are 24 PBT facilities in operation in the US [6]. With technological advancements, the American College of Radiology in collaboration with the American Association of Physicists in Medicine have developed technical standards and practice parameters for the performance of PBT services in the US. A proton quality assurance approach for specific machines is recommended because PBT equipment can be significantly different from other photon therapy equipment. For example, since the Bragg peak of a proton beam is narrower than a photon beam, the quality assurance tests performed by the medical physicist for a PBT machine require tighter limits than for a PRT LINAC. The types of dosimeters used by the Medical Physicist and Radiation Therapist for PBT will require new adapted approaches for dosimetry since the protons have different physical characteristics to photons.

Annual verification of the dose and credentialing by the Radiological Physics Centre (RPC) is mandatory when patients are entered on National Cancer Institute (NCI)-supported clinical trials. The Australian Clinical Dosimetry Service is a relevant body for verification of dose, and the equivalent of the RPC. It is recommended that a photon therapy institution that does not participate in NCI clinical trials nevertheless should obtain similar certification as evidence of compliance with basic dosimetry standards. Outlined credentialing recommendations also state that it is common practice in proton therapy facilities to divide the clinical care and radiation therapy activities among several individuals with different expertise. It is not expected that a single person will be an expert in all aspects of

operating a proton therapy facility but rather there is a requirement for a multidisciplinary team including:

- Physicians, such as radiation oncologists who are medical doctors specialising in radiation-based cancer treatment
- Medical physicists, who are responsible in areas of diagnosis and treatment of patients in close consultation with physician colleagues. They are also responsible for providing independent verification of the radiation dose performed.
- Radiation therapists, who develop the treatment plan for the radiation dose distributions and dose calculations used in treating diseased tissue. In Australia, development of the treatment plan is performed by RTs, medical physicists and radiation oncologists in combination.
  - Additionally, RTs, prepare patients for the delivery of their custom treatment plan, positioning them in the way that assures the proton beam hits its target
- Radiation oncology nurses, charged with patient care and monitoring before, during and after particle therapy sessions

These are the same requirements as for a PRT facility.

Like the US, Europe offers PBT services at sixteen facilities across nine countries (2017) [6]. The UK is currently in the process of introducing PBT for adult and children for the first time. The NHS England has commissioned PBT services to commence from August 2018 at the Christie NHS Foundation Trust in Manchester, and from 2020 at the University College London Hospitals in London. To allow the NHS service to increase its clinical expertise and capacity in a safe and controlled manner, it is anticipated that when the NHS service starts some patients requiring PBT will continue to be sent for treatment abroad, as is current practice (*Schedule 2 Service Specifications: Proton Beam Therapy Service - Adults and Children)*, April 2017, NHS England). At the same time, as construction progresses for UK's two new PBT centres, the NHS is developing best practice strategies for PBT staffing to ensure:

- adequate training of all staff delivering PBT
- adequate site specialist oncology staff are to be available on site with links to integrated multidisciplinary teams
- national standards for training and practice of the relevant professional bodies are met, on par with those set out by Royal College of Radiologists, Society and College of Radiographers, and Institute of Physics and Engineering in Medicine
- processes are in place for the management of risk to staff
- support programs are place for the professional development of UK's first PBT service workforce, for instance, training placements for UK PBT clinicians and technicians.

The National Symposium in Adelaide in November 2017 was the first time the tripartite group (Radiation oncologist, therapist and medical physicists) has come together to discuss planning for training in particle therapy. The groups outlined plans for training and there is a 5-year lag period before the first facility needs to be staffed.

Training will need to be in areas broader than the field of radiation oncology. For example, base of skull surgeons, ophthalmologists with experience and expertise in ocular tumours will need to be part of the broader time of specialists who manage patients suitable for treatment by particle therapy. There are specialists in these fields already; over time, as referral patterns change to accommodate particle therapy, common treatment pathways need to develop and there is needs to be a mechanism whereby super-specialised expertise is acknowledged.

F.2. ONGOING CLINICAL TRIALS

There are six RCTs currently being conducted in the USA and Germany Table 49). As previously mentioned in Section B, there is a lack of evidence on the comparative effectiveness and safety of conventional radiotherapy versus PBT. Review the outcomes of these RCTs once they are available could provide additional evidence.

Table 49   Profiles of RCTs currently in progress

Study ID	Study design	Level of evidence[a]	Location Setting	Study population characteristics	Description of intervention	Description of comparator	PICO outcomes assessed	Measurement of outcomes and methods of analysis
	Duration	Risk of bias assessment[b]	Length of follow-up	Population (patients with specific tumours)				
NCT00496119	comparative cohort RCT (phase II)	Level II	MD Anderson Cancer Centre, USA	estimated N=15, all ages and sexes eligible	PBT total dose of 70 Gy	PBT total dose of 70 Gy combined with PRT	disease-free and overall survival	TBD
	September 2006-September 2018	high risk of bias	until endpoint (disease progression or death)	chordomas				
NCT01182753	comparative cohort RCT (phase III)	Level II	University of Heidelberg, Germany	estimated N=154, age=18-80 years, all sexes eligible	PBT total dose of 50-56 Gy or 70 Gy based on two planning target volumes	CIT total dose of 45 or 60 Gy for based on two planning target volumes	disease-free survival, overall survival, local tumour control, safety (acute and late radiation-related toxicities)	TBD
	August 2010-August 2022	high risk of bias	5 years follow-up	(clival) chondrosarcomas				
NCT01182779	comparative cohort RCT (phase III)	Level II	University of Heidelberg, Germany	estimated N=319, age=18-80 years, all sexes eligible	PBT total dose of 50-56 or 72 Gy based on two planning target volumes	CIT total dose of 45 or 63 Gy based on two planning target volumes	disease-free survival, overall survival, local tumour control, safety (acute and late radiation-related toxicities)	TBD
	July 2010-August 2023	high risk of bias	8 years follow-up	(clival) chordomas				

Study ID	Study design	Level of evidence[a]	Location Setting	Study population characteristics	Description of intervention	Description of comparator	PICO outcomes assessed	Measurement of outcomes and methods of analysis
	Duration	Risk of bias assessment[b]	Length of follow-up	Population (patients with specific tumours)				
NCT01811394	comparative cohort RCT (phase II)	Level II	University of Heidelberg, Germany	estimated N=100, age=18-80 years, all sexes eligible	PBT total dose of 64 Gy	CIT total dose of 64 Gy	disease-free survival, overall survival, HRQoL, safety (radiation-related toxicities Grade 3-5)	TBD
	January 2013-June 2020	high risk of bias	1 year follow-up	(sacral) chordomas				
NCT02923570	comparative cohort RCT (phase II)	Level II	Memorial Sloan Kettering Cancer Centre, USA	estimated N=132, age=18 years or older, all sexes are eligible	PBT total dose of 60-66 Gy	IMRT total dose of 60-66 Gy	safety (radiation-related toxicities Grade 2 or higher)	TBD
	October 2016-October 2021	high risk of bias	1 year follow-up	head and neck tumours likely covering multiple PICO population inclusions				
NCT03164460	comparative cohort RCT (phase II)	Level II	MD Anderson Cancer Centre, USA	estimated N=100, >18 years of age, all sexes eligible	IMRT/IMPT total dose 66-77 Gy	SBRT total dose 45 Gy	safety (toxicities > grade 2), local tumour control, disease-free and overall survival, HRQoL	TBD
	May 2017-May 2022	high risk of bias	up to 2 years follow-up	inoperable head and neck tumours likely covering multiple PICO population inclusions				

Abbreviations: NR: Not reported, TBD: To be determined
Notes:
a NHMRC evidence hierarchy based on the GRADE system,
b risk of bias according to the Cochrane tool for assessing risk of bias in randomised trials.

F.3. PICO POPULATION

The agreed PICO Confirmation listed the following eleven patient groups since, at that time, these patients are eligible to access PBT under the MTO Program:

1. Chordoma of the axial skeleton (defined as the skull, vertebral column and bony pelvis)
2. Sarcoma of the axial skeleton
3. Paediatric CNS tumour
4. Ocular melanoma
5. Retinoblastoma
6. Soft tissue sarcoma in close proximity to the axial skeleton (to include rhabdomyosarcoma)
7. Adenoid cystic carcinoma of the lacrimal or salivary glands
8. Craniopharyngioma
9. Intracranial germ cell tumour
10. NeuroblastomaNephroblastomaHowever there are many more conditions which could be treated with PBT, including cancer of the lung, prostate, liver, bone, uterine cervix and pancreas [6]. When PBT facilities are operationalised in Australia, it is the best use of resources for the facilities to operate at maximum capacity. Therefore it is likely that there will be future Assessment Reports presented to MSAC for consideration of the reimbursement of PBT for other conditions.

Appendix A Clinical Experts and Assessment Group

CLINICAL EXPERTS

Name	Expertise
Dr Verity Ahern	Paediatric radiation oncology
Dr Hien Le	Radiation oncology

ASSESSMENT GROUP

HealthConsult

Name	Position
Joe Scuteri	Managing Director
Lisa Fodero	Director
Robert Kemp	Associate Director
Oona Reardon	Research Analyst
Roy Ramiscal	Consultant
Ms Suzanne Lyon	Manager

Noted conflicts of interest

Dr Verity Ahern is on the Steering Committee for the National Particle Treatment and Research Centre at Westmead.

Dr Hien Le is on the Steering Committee for the National Particle Treatment and Research Centre in Adelaide.

APPENDIX B   SEARCH STRATEGIES

BIBLIOGRAPHIC DATABASES

Electronic database	Time period searched
Embase	July to September 2017
Medline	July to September 2017
The Cochrane Library (CDSR, Central, HTA)	July to September 2017

ADDITIONAL SOURCES OF LITERATURE (INCLUDING WEBSITES)

Source	Location
ClinicalTrials.gov	https://clinicaltrials.gov/
National Institutes of Health (PubMed)	https://www.ncbi.nlm.nih.gov/
PBAC	www.pbs.gov.au
MBS	www.mbsonline.gov.au
ABS	www.abs.gov.au
American Brain Tumour Association	http://www.abta.org/
Independent Hospital Pricing Authority	https://www.ihpa.gov.au/
Australian Institute of Health and Welfare	https://www.aihw.gov.au/

APPENDIX C   STUDIES INCLUDED IN THE SYSTEMATIC REVIEW

Table C.1   Profiles of comparative studies (2014-2017) used in systematic review of clinical literature

Study	Study design	Level of evidence[a]	Location Setting	Study population characteristics	Description of intervention	Description of comparator	PICO outcomes assessed	Measurement of outcomes and methods of analysis
	Duration	Risk of bias assessment[b]	Length of follow-up	Population (patients with specific tumours)				
PICO 1: Brain, spinal and soft tissue cancers								
Molina C.A. et al., 2014	retrospective comparative effectiveness	Level III	multi-institutional series	N=16, mean age=55 years, 43.8% male	post-surgery PBT/IMRT (radiation dosage NR), N=9	surgery alone, N=7	overall survival	Kaplan-Meier
	2000-2008	critical risk of bias	4.6 years mean follow-up	chordomas				
Mima M. et al., 2014	retrospective comparative effectiveness	Level III	Hyogo Ion Beam Medical Centre, Japan	N=23, median age=72 years, 65% male	PBT total dose of 70.2 Gy/4.4 or 2.2 Gy per Fr, N=7	CIT total dose of 70.2 Gy/4.4 or 2.2 Gy per Fr, N=16	local tumour control, overall survival	Kaplan-Meier
	2005-2011	critical risk of bias	3.2 years median follow-up	chordoma (sacral)				
Rotondo R.L. et al., 2015	retrospective comparative effectiveness	Level III	Massachusetts General Hospital, USA	N=126, mean age=53.2, 62.2% male	combined adjuvant PBT and PRT post-surgery, mean total dose 73.7 GyE/1.8-2 Gy per Fr, N=58	PBT combined with photon pre- and post-surgery accrued to 71.0 GyE /1.8-2 Gy per Fr, N=60	local tumour control, overall survival, safety (RT-specific toxicities, radiation dose)	Kaplan-Meier was sued for local control and survival rates. Log-rank test was used to compare RT doses.
	1982-2011	critical risk of bias	3.4 years median follow-up	chordoma (spinal)				
Indelicato D.J. et al., 2016	retrospective comparative effectiveness	Level III	University of Florida, USA	N=51, 37% female, median age=58 years	PBT median total dose of 70.2 GyE/1.2 or 1.8 GyE per Fr, N=28	PBT combined with IMRT median total dose of 70.2 GyE/1.2 or 1.8 GyE per Fr, N=23	local tumour control	Log-rank test was used to test effects of RT modality and radiation fractionation on local control
	2007-2013	critical risk of bias	3.7 years mean follow-up	66.7% chordomas, 33.3% chondrosarcomas				

Study	Study design	Level of evidence[a]	Location Setting	Study population characteristics	Description of intervention	Description of comparator	PICO outcomes assessed	Measurement of outcomes and methods of analysis
	Duration	Risk of bias assessment[b]	Length of follow-up	Population (patients with specific tumours)				
PICO 2: Ocular cancers								
Schonfeld S. et al., 2014	retrospective comparative effectiveness	Level III	Helmholtz-Zentrum Berlin, Germany	N=62, mean age= 57.7, 53.2% male	PBT total dose of 60 GyE/15 GyE per Fr, N=18	surgery with PBT total dose of 60 GyE/15 GyE per Fr, N=44	disease-related mortality, incidence of metastasis, local tumour control, patient-relevant outcomes (visual acuity), safety (secondary glaucoma, cataract formation)	Kaplan-Meier sued for rates of metastasis, disease-related mortality, local tumour control, glaucoma and cataract incidence. Visual acuity was measured by Box-Whisker distribution
	1998-2005	critical risk of bias	5.86 years median follow-up	ocular (choroidal) melanoma				
Sikuade M. et al., 2015	retrospective comparative effectiveness	Level III	Sheffield Ocular Oncology Service, UK	N=191, mean age=60 years, 62.8% males	PBT total dose of 58.4 Gy/14.6 GyE per Fr, N=106	SRS total dose of 35 Gy as 1 Fr, N=85	overall survival, patient-relevant outcomes (visual acuity), safety (RT-related toxicity)	Student's t-test
	2001-2011	critical risk of bias	2.8 years and 3.25 years mean follow-up for PBT and comparator cohorts, respectively	ocular (choroidal) melanoma				
Seibel I. et al., 2017	retrospective comparative effectiveness	Level III	Charite-Universitatsmedizin Berlin, Germany	N=2499, median age=61 years, 53% male	PBT total dose of 60 CGE/15 CGE per Fr, N=216	endoresection after PBT total dose of 60 CGE/15 CGE per Fr, N=445 endodrainage-vitrectomy after PBT total dose of 60 CGE/15 CGE per Fr, N=242	enucleation-free survival, safety (RT-related toxicity)	Kaplan-Meier
	1998-2015	critical risk of bias	4.3 years median follow-up	ocular (choroidal or ciliary body) melanoma				

Study	Study design	Level of evidence[a]	Location Setting	Study population characteristics	Description of intervention	Description of comparator	PICO outcomes assessed	Measurement of outcomes and methods of analysis
	Duration	Risk of bias assessment[b]	Length of follow-up	Population (patients with specific tumours)				
PICO 3: Paediatric and adolescent cancers								
Sethi R. et al., 2014	retrospective comparative effectiveness	Level III	Harvard Cyclotron Laboratory or the Massachusetts General Hospital, USA	N=86, median age=8.5 years and 13.1 years for PBT and comparator cohorts, 47.7% male	PBT median total dose of 44.16 Gy +/- chemotherapy. PBT dose per Fr NR, N=55	PRT median total dose of 45 Gy +/- chemotherapy, PRT dose per Fr NR, N=31	incidence of distant metastasis, safety (rate of in-field or RT-related secondary malignancies)	cumulative incidence of secondary malignancy was estimated by the Kaplan- Meier
	1986-2011	critical risk of bias	6.9 years and 13.1 years median follow-up for PBT and comparator cohorts, respectively	retinoblastoma				
Bishop A.J. et al., 2014	retrospective comparative effectiveness	Level III	MD Anderson Cancer Centre, USA	N=52, median age= 8.9 years, 44% male	surgery + PBT median total dose of 50.4 Gy/1.8 Gy per Fr, N=21	surgery + IMRT median total dose of 50.4 Gy/1.8 Gy per Fr, N=31	overall survival, safety (RT-related toxicities)	Fisher's exact test was used to compare toxicity incidence rates between cohorts, Kaplan-Meier was used to calculated overall survival rates
	1996-2012	critical risk of bias	5 years median follow-up	craniopharyngioma				
Yock T.I. et al., 2014	retrospective comparative effectiveness	Level III	Massachusetts General Hospital or Lucile Packard Children's Hospital, USA	N=120, median age= 7 years and 7.7 years for PBT and comparator cohorts, respectively, 53.3% male	PBT total dose of 50-54 Gy for 71% of cohort +/- surgery +/- chemotherapy, N=57	PRT total dose of 50-54 Gy for 71% of cohort +/- surgery +/- chemotherapy, N=63	HRQoL	PedsQL Core Scale
	1998-2007	critical risk of bias	3 years median follow-up	paediatric CNS tumours				
Song S. et al., 2014	prospective comparative effectiveness	Level III	National Cancer Centre, Korea	N=39, median age =10 years, 55.8% male	chemotherapy +/- PBT mean total dose of 51.8 Gy. PBT dose per Fr NR, N=30	chemotherapy +/- PRT mean total dose of 53.2 Gy/ PRT dose per Fr NR, N=13	patient-relevant outcomes (freedom from blood product transfusion), safety	Fisher's exact test was used to compare categorical variables between cohorts, unpaired Student's t-
	2008-2012	critical risk of bias	1.8 years median follow-up	paediatric CNS tumours				

Study	Study design	Level of evidence[a]	Location Setting	Study population characteristics	Description of intervention	Description of comparator	PICO outcomes assessed	Measurement of outcomes and methods of analysis
	Duration	Risk of bias assessment[b]	Length of follow-up	Population (patients with specific tumours)				
							(acute radiation-related toxicities)	test or Mann-Whitney U-test was used to compare continuous variable between the cohorts
Gunther J.R et al., 2015	retrospective comparative effectiveness	Level III	MD Anderson Cancer Centre, USA	N=72, ages are unmatched, genders are NR	surgery before chemotherapy + PBT median total dose of 59.4 Gy. PBT dose per Fr NR, N=37	surgery before chemotherapy + IMRT median total dose of 54. IMRT dose per Fr, N=35	overall survival, recurrence rate, safety (acute and late RT-related toxicities)	Kaplan-Meier
	2000-2013	critical risk of bias	3.4 years median follow-up	paediatric CNS tumours (intracranial ependymoma)				
Eaton B.R. et al., 2016	prospective comparative effectiveness	Level III	Massachusetts General Hospital, USA	N=88, median age=6.2 years and 8.2 years for PBT and comparator cohorts, respectively, 61.4% male	surgery before PBT total dose of 54-55.8 Gy/1.8 Gy per Fr, N=45	surgery before PRT total dose of 54-55.8 Gy/1.8 Gy per Fr, N=43	overall survival, local tumour control, safety (radiation dose)	Kaplan-Meier was used to estimate survival and local control rates. Multivariate analysis was used to determine linkages with RT dosage
	2000-2009	critical risk of bias	6.2 years median follow-up	paediatric CNS tumours (medulloblastoma)				
Eaton B.R. et al., 2016	retrospective comparative effectiveness	Level III	Massachusetts General Hospital, USA	N=77, median age=6.2 and 8.3 years for PBT and photon cohorts, respectively, 58.4% male	surgery + chemotherapy + PBT total dose of 54-55.8 Gy/1.8 Gy per Fr, N=40	surgery + chemotherapy + PRT total dose of 54-55.8 Gy/1.8 Gy per Fr, N=36	patient-relevant outcomes (changes in height and BMI), safety (radiation dose, systemic effects eg. endocrinopathy)	Chi-square or Fisher's exact test was used to compare systemic effects between cohorts. ANOVA or Spearman's rank correlation was used to assess changes to height and BMI. Univariate analysis was used for linkages with RT dosage
	2000-2009	critical risk of bias	5.8 years and 7 years median follow-up for PBT and photon cohorts, respectively	paediatric CNS tumours (medulloblastoma)				

Study	Study design	Level of evidence[a]	Location Setting	Study population characteristics	Description of intervention	Description of comparator	PICO outcomes assessed	Measurement of outcomes and methods of analysis
	Duration	Risk of bias assessment[b]	Length of follow-up	Population (patients with specific tumours)				
Sato M. et al., 2017	retrospective comparative effectiveness	Level III	Texas Children's Cancer Centre, USA	N=79, median age=3.7 years, 58.2% male	post-operative PBT median total dose of 55.8 Gy/1.8 Gy per Fr, N=41	post-operative IMRT, median total dose of 54 Gy/1.8 Gy per Fr, N=38	overall survival, disease progression, local recurrence rate, safety (RT-related toxicities)	Kaplan-Meier
	2000-2013	critical risk of bias	2.6 years and 4.9 years median follow-up for PBT and IMRT cohorts, respectively	paediatric CNS tumours (ependymomas)				
PICO 4: Other PICO-relevant cancers								
Takagi M. et al., 2014	retrospective comparative effectiveness	Level III	Hyogo Ion Beam Medical Centre, Japan	N=11, age range=24-83, 34% male	PBT mean total dose of 67.0 GyE/2.5-3.6 GyE per Fr +/- surgery, N=6	CIT mean total dose of 63.9 GyE/2.5-3.6 GyE per Fr +/- surgery, N=5	local tumour control, overall survival, disease progression, safety (acute and late RT-related toxicities)	Kaplan-Meier was used to assess local tumour control, overall survival, disease progression
	2002-2012	critical risk of bias	3.2 years median follow-up	salivary gland adenoid cystic carcinoma				
Romesser P.B. et al., 2016	retrospective comparative effectiveness	Level III	Memorial Sloan Kettering Cancer Centre, USA	N=41, median age=60.9 years, 22.2% undergoing concurrent chemotherapy	PBT median median total dose of 66 Gy/2 Gy per Fr, N=18	IMRT median total dose of 66 Gy/2 Gy per Fr, N=23	local tumour control, overall survival, incidence of metastases, safety (acute RT-related toxicities, radiation dose)	RT dose and toxicity characteristics were compared either by Chi-square or 2-tailed Student's t-test. 1-year rates for tumour control, distant metastases and overall survival were calculated using Kaplan-Meier
	2011-2014	critical risk of bias	8.7 months median follow-up	salivary gland carcinoma				

Notes: [a] NHMRC evidence hierarchy based on the GRADE system [b] risk of bias according to the ROBINS-I tool for assessing risk of bias in non-randomised studies of interventions

Abbreviations: ANOVA, Analysis of variance model software; CIT, carbon ion therapy; CNS, central nervous system; Fr, fractions; IMRT, intensity modulated radiotherapy; NR, not reported; PBT, proton beam therapy; PRT, photon radiotherapy; RT, radiotherapy

APPENDIX D   EXCLUDED STUDIES

Below is a list of full-text publications excluded from the clinical evaluation evidence base collected in Section B. Reasons for exclusion are italicised.

Ahmed R, Sheybani A, Menezes AH, Buatti JM, Hitchon PW. Disease outcomes for skull base and spinal chordomas: a single centre experience. Clinical neurology and neurosurgery 2015; 130: 67-73.
> *Outcomes of are confounded, unclear, and/or not reported for individual study arms including PBT intervention*

Chargari C, Magne N, Guy J-P, et al. Optimize and refine therapeutic index in radiation therapy: Overview of a century. Cancer Treatment Reviews, 2016.
> *Not a systematic review but a literature review.*

Eaton BR, Chowdhry V, Weaver K, et al. Use of proton therapy for re-irradiation in pediatric intracranial ependymoma. Radiother Oncol 2015; 116(2): 301-8.
> *Outcomes of are confounded, unclear, and/or not reported for individual study arms including PBT intervention*

Eaton BR, Yock T. The use of proton therapy in the treatment of benign or low-grade pediatric brain tumors. Cancer J 2014; 20(6): 403-8.
> *Not a systematic review but a literature review.*

Farnia B, Allen PK, Brown PD, et al. Clinical outcomes and patterns of failure in pineoblastoma: a 30-year, single-institution retrospective review. World Neurosurg 2014; 82(6): 1232-41.
> *Outcomes of are confounded, unclear, and/or not reported for individual study arms including PBT intervention*

Gokaslan ZL, Zadnik PL, Sciubba DM, et al. Mobile spine chordoma: results of 166 patients from the AOSpine Knowledge Forum Tumor database. J Neurosurg Spine 2016; 24(4): 644-51.
> *Outcomes of are confounded, unclear, and/or not reported for individual study arms including PBT intervention*

Grant SR, Grosshans DR, Bilton SD, et al. Proton versus conventional radiotherapy for pediatric salivary gland tumors: Acute toxicity and dosimetric characteristics. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology 2015; 116(2): 309-15.
> *No clear efficacy outcome measures.*

Greenberger BA, Pulsifer MB, Ebb DH, et al. Clinical outcomes and late endocrine, neurocognitive, and visual profiles of proton radiation for pediatric low-grade gliomas. Int J Radiat Oncol Biol Phys 2014; 89(5): 1060-8.

Outcomes of are confounded, unclear, and/or not reported for individual study arms including PBT intervention

Grosshans DR, Zhu XR, Melancon A, et al. Spot scanning proton therapy for malignancies of the base of skull: treatment planning, acute toxicities, and preliminary clinical outcomes. Int J Radiat Oncol Biol Phys 2014; 90(3): 540-6.

Outcomes of are confounded, unclear, and/or not reported for individual study arms including PBT intervention

Husak AI, Bridge P. Proton therapy in craniospinal irradiation: a systematic review. Journal of Radiotherapy in Practice 2015; 15(02): 196-202.

Does not report on relevant outcome measures in detail.

Indelicato DJ, Bradley JA, Sandler ES, et al. Clinical outcomes following proton therapy for children with central nervous system tumors referred overseas. Pediatr Blood Cancer 2017.

Outcomes of are confounded, unclear, and/or not reported for individual study arms including PBT intervention

Kim IK, Lane AM, Jain P, Awh C, Gragoudas ES. Ranibizumab for the Prevention of Radiation Complications in Patients Treated With Proton Beam Irradiation for Choroidal Melanoma. Trans Am Ophthalmol Soc. 2016; 114: T2.

The only RCT completed and published after 2014 but examined PBT monotherapy against an invalid PICO comparator – anti-angiogenesis immunotherapy may be used to supplement PBT but is not a standalone treatment for ocular melanomas itself.

Leeman JE, Romesser PB, Zhou Y, et al. Proton therapy for head and neck cancer: expanding the therapeutic window. Lancet Oncol 2017; 18(5): e254-e65.

Not a systematic review but a literature review.

McDonald MW, Plankenhorn DA, McMullen KP, et al. Proton therapy for atypical meningiomas. J Neurooncol 2015; 123(1): 123-8.

Outcomes of are confounded, unclear, and/or not reported for individual study arms including PBT intervention

Morimoto K, Demizu Y, Hashimoto N, et al. Particle radiotherapy using protons or carbon ions for unresectable locally advanced head and neck cancers with skull base invasion. Jpn J Clin Oncol 2014; 44(5): 428-34.

Outcomes of are confounded, unclear, and/or not reported for individual study arms including PBT intervention

Mozes P, Dittmar JO, Habermehl D, et al. Volumetric response of intracranial meningioma after photon or particle irradiation. Acta Oncol 2017; 56(3): 431-7.
Meningiomas in adults does not conform to any pre-defined PICO population.

Phan J, Sio TT, Nguyen TP, et al. Reirradiation of Head and Neck Cancers With Proton Therapy: Outcomes and Analyses. Int J Radiat Oncol Biol Phys 2016; 96(1): 30-41.
Partially defined PICO population.

Seibel I, Cordini D, Rehak M, et al. Local Recurrence After Primary Proton Beam Therapy in Uveal Melanoma: Risk Factors, Retreatment Approaches, and Outcome. Am J Ophthalmol 2015; 160(4): 628-36.

All study arms received PBT primary treatment. Intervention cohort too small with N < 1 for PBT retreatment of recurring ocular melanomas in contrast to comparators: thermotherapy (N=7), brachytherapy (N=8), and enucleation (N=19).

Verma V, Mishra MV, Mehta MP. A systematic review of the cost and cost-effectiveness studies of proton radiotherapy. Cancer 2016; 122(10): 1483-501.

Does not systematically review primary sources of clinical data (eg. RCTs and comparative cohort studies).

REFERENCES

1. Atkins, D., et al., 2004, Grading quality of evidence and strength of recommendations. *BMJ*. **328**(7454): p. 1490.
2. (HTA), H.T.A.P. and W.S.H.C. Authority, 2014, Proton Beam Therapy: Final Evidence Report.
3. Smith, A.R., 2009, Vision : Proton therapy. **36**(2): p. 556-568.
4. Paganetti, H., 2002, Nuclear interactions in proton therapy: dose and relative biological effect distributions originating from primary and secondary particles. *Phys Med Biol*. **47**(5): p. 747-64.
5. Mohan, R. and D. Grosshans *Proton therapy - Present and future*. Advanced drug delivery reviews, 2017. **109**, 26-44 DOI: 10.1016/j.addr.2016.11.006.
6. (2017), Health Policy Advisory Committee on Technology, 2017, Proton and Heavy Ion Therapy: An overview.
7. Institute for Clinical and Economic Review (ICER), *Proton Beam Therapy: Final Evidence Report, Washington State Health Care Authority - Health Technology Assessment*. 2014: Olympia, WA, USA.
8. Widder, J., et al., 2016, The Quest for Evidence for Proton Therapy: Model-Based Approach and Precision Medicine. *Int J Radiat Oncol Biol Phys*. **95**(1): p. 30-6.
9. Patel, S., et al., 2014, Recommendations for the referral of patients for proton-beam therapy, an Alberta Health Services report: a model for Canada? *Curr Oncol*. **21**(5): p. 251-62.
10. Party., C.C.A.S.G.W. *Clinical practice guidelines for the management of adult onset sarcoma*. 2014 October 2014 [cited 2017 1 November]; Clinical practice guidelines for the management of adult onset sarcoma]. Available from: http://wiki.cancer.org.au/australia/Guidelines:Sarcoma/Foreword.
11. Zoicas, F. and C. Schofl, 2012, Craniopharyngioma in adults. *Front Endocrinol (Lausanne)*. **3**: p. 46.
12. Jovanovic, P., et al., 2013, Ocular melanoma: an overview of the current status. *Int J Clin Exp Pathol*. **6**(7): p. 1230-44.
13. Welfare, A.I.o.H.a., *A picture of Australia's children 2009*. 2009, AIHW: Canberra.
14. Venkitaraman, R., et al., 2008, Primary Adenoid Cystic Carcinoma Presenting as an Orbital Apex Tumor. *Neuroophthalmology*. **32**(1): p. 27-32.
15. International Association for the Study of Lung Cancer (IASLC). *Proton-Beam Therapy Versus Photon-Beam Therapy: The Debate Continues*. 2017 14 August 2018]; Available from: http://www.lungcancernews.org/2017/09/29/proton-beam-therapy-versus-photon-beam-therapy-the-debate-continues/.
16. McGowan, S.E., N.G. Burnet, and A.J. Lomax, 2013, Treatment planning optimisation in proton therapy. *Br J Radiol*. **86**(1021): p. 20120288.
17. Grosshans, D.R., et al., 2017, The role of image-guided intensity modulated proton therapy in glioma. *Neuro Oncol*. **19**(suppl_2): p. ii30-ii37.
18. National Health and Medical Research Council (NHMRC), *How to use the evidence: assessment and application of scientific evidence*. 2000.
19. Whiting, P., et al., 2016, ROBIS: A new tool to assess risk of bias in systematic reviews was developed. *Journal of clinical epidemiology*. **69**: p. 225-34.
20. Higgins, J.P., et al., 2011, The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. **343**: p. d5928.
21. Sterne, J.A., et al., 2016, ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. **355**: p. i4919.

22. Canadian Agency for Drugs and Technologies in Health (CADTH), *Proton Beam Therapy for the Treatment of Cancer in Children and Adults, Health Technology Assessment*. 2017: Ottawa, Ontario, Canada.

23. Fossati, P., et al., 2016*,* Review of photon and proton radiotherapy for skull base tumours*. Rep Pract Oncol Radiother*. **21**(4): p. 336-55.

24. Laprie, A., et al., 2015*,* Paediatric brain tumours: A review of radiotherapy, state of the art and challenges for the future regarding protontherapy and carbontherapy*. Cancer radiotherapie : journal de la Societe francaise de radiotherapie oncologique*. **19**(8): p. 775-89.

25. Leroy, R., et al., 2016*,* Proton Therapy in Children: A Systematic Review of Clinical Effectiveness in 15 Pediatric Cancers*. Int J Radiat Oncol Biol Phys*. **95**(1): p. 267-78.

26. Matloob, S.A., H.A. Nasir, and D. Choi, 2016*,* Proton beam therapy in the management of skull base chordomas: systematic review of indications, outcomes, and implications for neurosurgeons*. Br J Neurosurg*. **30**(4): p. 382-7.

27. Verma, V. and M.P. Mehta, 2016*,* Clinical Outcomes of Proton Radiotherapy for Uveal Melanoma*. Clin Oncol (R Coll Radiol)*. **28**(8): p. e17-27.

28. Molina, C.A., et al., 2014*,* Outcomes following attempted en bloc resection of cervical chordomas in the C-1 and C-2 region versus the subaxial region: a multiinstitutional experience*. J Neurosurg Spine*. **21**(3): p. 348-56.

29. Mima, M., et al., 2014*,* Particle therapy using carbon ions or protons as a definitive therapy for patients with primary sacral chordoma*. Br J Radiol*. **87**(1033): p. 20130512.

30. Rotondo, R.L., et al., 2015*,* High-dose proton-based radiation therapy in the management of spine chordomas: outcomes and clinicopathological prognostic factors*. J Neurosurg Spine*. **23**(6): p. 788-97.

31. Indelicato, D.J., et al., 2016*,* A Prospective Outcomes Study of Proton Therapy for Chordomas and Chondrosarcomas of the Spine*. Int J Radiat Oncol Biol Phys*. **95**(1): p. 297-303.

32. Schonfeld, S., et al., 2014*,* Proton beam therapy leads to excellent local control rates in choroidal melanoma in the intermediate fundus zone*. Am J Ophthalmol*. **158**(6): p. 1184-91.

33. Sikuade, M.J., et al., 2015*,* Outcomes of treatment with stereotactic radiosurgery or proton beam therapy for choroidal melanoma*. Eye (Lond)*. **29**(9): p. 1194-8.

34. Seibel, I., et al., 2017*,* Adjuvant Ab Interno Tumor Treatment After Proton Beam Irradiation*. Am J Ophthalmol*. **178**: p. 94-100.

35. Sethi, R.V., et al., 2014*,* Second nonocular tumors among survivors of retinoblastoma treated with contemporary photon and proton radiotherapy*. Cancer*. **120**(1): p. 126-33.

36. Bishop, A.J., et al., 2014*,* Proton beam therapy versus conformal photon radiation therapy for childhood craniopharyngioma: multi-institutional analysis of outcomes, cyst dynamics, and toxicity*. International journal of radiation oncology, biology, physics*. **90**(2): p. 354-61.

37. Yock, T.I., et al., 2014*,* Quality of life outcomes in proton and photon treated pediatric brain tumor survivors*. Radiother Oncol*. **113**(1): p. 89-94.

38. Song, S., et al., 2014*,* Proton beam therapy reduces the incidence of acute haematological and gastrointestinal toxicities associated with craniospinal irradiation in pediatric brain tumors*. Acta oncologica*. **53**(9): p. 1158-64.

39. Gunther, J.R., et al., 2015*,* Imaging Changes in Pediatric Intracranial Ependymoma Patients Treated With Proton Beam Radiation Therapy Compared to Intensity Modulated Radiation Therapy*. International journal of radiation oncology, biology, physics*. **93**(1): p. 54-63.

40. Eaton, B.R., et al., 2016, Clinical Outcomes Among Children With Standard-Risk Medulloblastoma Treated With Proton and Photon Radiation Therapy: A Comparison of Disease Control and Overall Survival. *International journal of radiation oncology, biology, physics*. **94**(1): p. 133-8.

41. Eaton, B.R., et al., 2016, Endocrine outcomes with proton and photon radiotherapy for standard risk medulloblastoma. *Neuro Oncol*. **18**(6): p. 881-7.

42. Sato, M., et al., 2017, Progression-free survival of children with localized ependymoma treated with intensity-modulated radiation therapy or proton-beam radiation therapy. *Cancer*. **123**(13): p. 2570-2578.

43. Takagi, M., et al., 2014, Treatment outcomes of particle radiotherapy using protons or carbon ions as a single-modality therapy for adenoid cystic carcinoma of the head and neck. *Radiother Oncol*. **113**(3): p. 364-70.

44. Romesser, P.B., et al., 2016, Proton beam radiation therapy results in significantly reduced toxicity compared with intensity-modulated radiation therapy for head and neck tumors that require ipsilateral radiation. *Radiother Oncol*. **118**(2): p. 286-92.

45. Ollendorf, D.A., Colby, J. A.& Pearson, S. D, 2014, Proton Beam Therapy: Final evidence report, Health Technology Assessment Program, Washington State Health Care Authority, Olympia, Washington State, USA.

46. Canadian Agency for Drugs and Technologies in Health (CADTH), *Proton Beam Therapy versus Photon Radiotherapy for Adult and Pediatric Oncology Patients: A Review of the Clinical and Cost-Effectiveness - Rapid Response*. 2016: Ottawa, Ontario, Canada.

47. Canadian Agency for Drugs and Technologies in Health {CADTH}, 2017, Proton Beam Therapy for the Treatment of Cancer in Children and Adults

48. Verma, V., M.V. Mishra, and M.P. Mehta, 2016, A systematic review of the cost and cost-effectiveness studies of proton radiotherapy. *Cancer*. **122**(10): p. 1483-501.

49. Glimelius, B., et al., 2005, Number of patients potentially eligible for proton therapy. *Acta Oncol*. **44**(8): p. 836-49.

50. Barton, M.B., et al., 2014, Estimating the demand for radiotherapy from the evidence: a review of changes from 2003 to 2012. *Radiother Oncol*. **112**(1): p. 140-4.

51. Aldulaymi, B., et al., 2010, High plasma TIMP-1 and serum CEA levels during combination chemotherapy for metastatic colorectal cancer are significantly associated with poor outcome. *Oncology*. **79**(1-2): p. 144-9.

52. Chung, C.S., et al., 2013, Incidence of second malignancies among patients treated with proton versus photon radiation. *Int J Radiat Oncol Biol Phys*. **87**(1): p. 46-52.

53. Miralbell, R., et al., 1997, Potential role of proton therapy in the treatment of pediatric medulloblastoma/primitive neuroectodermal tumors: reduction of the supratentorial target volume. *Int J Radiat Oncol Biol Phys*. **38**(3): p. 477-84.

54. Lundkvist, J., et al., 2005, Cost-effectiveness of proton radiation in the treatment of childhood medulloblastoma. *Cancer*. **103**(4): p. 793-801.

55. Rwigema, J.C., et al., 2017, Proton Therapy Improves Toxicity for Oropharyngeal Cancer: An Outcomes and Predictive Model-based Approach. *International Journal of Radiation Oncology*Biology*Physics*. **Volume 99,** (Issue 2, Supplement, 1 October 2017,): p. Pages S135-S136.

56. Rwigema, J.C., et al., 2017, Proton Therapy Improves Toxicity for Oropharyngeal Cancer: An Outcomes and Predictive Model-based Approach. *International Journal of Radiation Oncology*Biology*Physics*. **99**(2, Supplement): p. S135-S136.

57. Duncan, W., 1994, An evaluation of the results of neutron therapy trials. *Acta Oncol*. **33**(3): p. 299-306.

58. Mailhot Vega, R.B., et al., 2013, Cost effectiveness of proton therapy compared with photon therapy in the management of pediatric medulloblastoma. *Cancer*. **119**(24): p. 4299-307.

Assessment name – MSAC CA PBT 1455

59.   Peeters, A., et al., 2010, How costly is particle therapy? Cost analysis of external beam radiotherapy with carbon-ions, protons and photons. *Radiother Oncol*. **95**(1): p. 45-53.

60.   Vanderstraeten, B., et al., 2014, In search of the economic sustainability of Hadron therapy: the real cost of setting up and operating a Hadron facility. *Int J Radiat Oncol Biol Phys*. **89**(1): p. 152-60.

61.   Argarwal, A., 2014, Affordability of cancer care in the United Kingdom – Is it time to introduce user charges? *Cancer Policy*. **June 2014 Volume 2**(2): p. 31-39.

62.   Technology, H.P.A.C.o., 2017, Proton and Heavy Ion Therapy: An Overview.

63.   Epstein, K., 2012, Is spending on proton beam therapy for cancer going too far, too fast? *BMJ*. **344**: p. e2488.

64.   Johnstone, P.A., J. Kerstiens, and H. Richard, 2012, Proton facility economics: the importance of "simple" treatments. *J Am Coll Radiol*. **9**(8): p. 560-3.

65.   *Proton beam therapy (Structured abstract)*. Health Technology Assessment Database, 2014.

66.   Goitein, M. and M. Jermann, 2003, The relative costs of proton and X-ray radiation therapy. *Clin Oncol (R Coll Radiol)*. **15**(1): p. S37-50.

67.   Verma, V., C.B. Simone, 2nd, and M.V. Mishra, 2018, Quality of Life and Patient-Reported Outcomes Following Proton Radiation Therapy: A Systematic Review. *J Natl Cancer Inst*. **110**(4).

68.   Kuhlthau, K.A., et al., 2012, Prospective study of health-related quality of life for children with brain tumors treated with proton radiotherapy. *J Clin Oncol*. **30**(17): p. 2079-86.

69.   Weber, D.C., et al., 2015, Tumor control and QoL outcomes of very young children with atypical teratoid/rhabdoid tumor treated with focal only chemo-radiation therapy using pencil beam scanning proton therapy. *J Neurooncol*. **121**(2): p. 389-97.

70.   Moriarty, J.P., et al., 2015, Cost-effectiveness of proton beam therapy for intraocular melanoma. *PLoS One*. **10**(5): p. e0127814.

71.   Frisch, S. and B. Timmermann, 2017, The Evolving Role of Proton Beam Therapy for Sarcomas. *Clin Oncol (R Coll Radiol)*. **29**(8): p. 500-506.

72.   Miralbell, R., A. Lomax, and M. Russo, 1997, Potential role of proton therapy in the treatment of pediatric medulloblastoma/primitive neuro-ectodermal tumors: spinal theca irradiation. *Int J Radiat Oncol Biol Phys*. **38**(4): p. 805-11.

73.   Packer, R.J., et al., 2006, Phase III study of craniospinal radiation therapy followed by adjuvant chemotherapy for newly diagnosed average-risk medulloblastoma. *J Clin Oncol*. **24**(25): p. 4202-8.

74.   Hirano, E., et al., 2014, Cost-effectiveness analysis of cochlear dose reduction by proton beam therapy for medulloblastoma in childhood. *J Radiat Res*. **55**(2): p. 320-7.

75.   Marseille, E., et al., *Thresholds for the cost–effectiveness of interventions: Alternative approaches*. Vol. 93. 2015. 118-24.

76.   Lundkvist, J., et al., 2005, Proton therapy of cancer: potential clinical advantages and cost-effectiveness. *Acta Oncol*. **44**(8): p. 850-61.

77.   Ramaekers, B.L., et al., 2013, Protons in head-and-neck cancer: bridging the gap of evidence. *Int J Radiat Oncol Biol Phys*. **85**(5): p. 1282-8.

78.   Thaker, N.G., S.J. Frank, and T.W. Feeley, 2015, Comparative costs of advanced proton and photon radiation therapies: lessons from time-driven activity-based costing in head and neck cancer. *J Comp Eff Res*. **4**(4): p. 297-301.

79.   Orenstein, B., 2015, Proton therapy and cost. *Radiol Today*. **16**(2): p. 22.

80.   Grutters, J.P., et al., 2011, When to wait for more evidence? Real options analysis in proton therapy. *Oncologist*. **16**(12): p. 1752-61.

81. Parthan, A., et al., 2012, Comparative cost-effectiveness of stereotactic body radiation therapy versus intensity-modulated and proton radiation therapy for localized prostate cancer. *Front Oncol*. **2**: p. 81.

82. Center, A.C., 2015, Proton Beam Radiation Therapy for Intraocular and Periocular Retinoblastoma.

83. Center, M.D.A.C., 2017, Randomized Trial of Intensity-Modulated Proton Beam Therapy (IMPT) Versus Intensity-Modulated Photon Therapy (IMRT) for the Treatment of Oropharyngeal Cancer of the Head and Neck.

84. Center, M.S.K.C., 2017, Study of Proton Versus Photon Beam Radiotherapy in the Treatment of Head and Neck Cancer.

85. Merchant, T.E., et al., 2014, Effect of cerebellum radiation dosimetry on cognitive outcomes in children with infratentorial ependymoma. *Int J Radiat Oncol Biol Phys*. **90**(3): p. 547-53.

86. Luca Lorenzoni, F.K., International Comparisons of Health Prices and Volumes: New Findings. *OECD Publications*.

87. Independent Hospital Pricing Authority, *National Efficient Price Determination, report*. 2017.

88. Rose, P. and D. Campbell, *The Education Role: Patient Education Strategies in Ambulatory Care Settings*, in *Cancer Forum*. 2001, The QLD radium Institute, The Princess Alexandra Hospital: Queensland Australia.