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Public Summary Document

Application No. 1638 – Proton beam therapy for paediatric   
and rare cancers

**Applicant: South Australian Health and Medical Research Institute**

**Date of MSAC consideration: MSAC 80th Meeting, 26-27 November 2020**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](http://www.msac.gov.au/)

# Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of proton beam therapy (PBT) for adult patients with a rare cancer of the head or spine or paediatric and adolescent/young adult (AYA) patients with a solid tumour located in the head, neck or trunk of the body was received from the South Australian Health and Medical Research Institute (SAHMRI) by the Department of Health.

# MSAC’s advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC supported the creation of new Medicare Benefits Schedule (MBS) items for proton beam therapy (PBT) for specified rare cancers in paediatric, adolescent and young adult (AYA), and adult populations. MSAC acknowledged the limitations in the strength of the evidence available, but accepted that PBT had superior safety and non-inferior effectiveness compared to photon radiation therapy (PRT) in the specified rare cancers and populations. MSAC considered that the estimates of cost-effectiveness were uncertain due to limitations in the evidence, but accepted that by sufficiently decreasing the rates of toxicity events across these patient groups, PBT would result in sufficient net improvements in quality of life and cost offsets from reduced provision of health care resources.

MSAC recommended that the rare cancers be specified in the item descriptors for PBT, that a comparison of PBT and PRT plans be required to confirm a patient’s eligibility for PBT, and that data be collected prospectively for patients treated with PRT (starting as soon as possible and enrolling patients until the Australian Bragg Centre becomes operational) and for patients treated with PBT once the Bragg Centre starts treating patients. In addition, MSAC advised on a number of outstanding implementation issues and therefore requested MSAC be informed of the Department’s progress in resolving these issues prior to the MBS listing of PBT to ensure the service is implemented nationally in an equitable way to the eligible population.

| **Consumer summary** |
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| The South Australian Health and Medical Research Institute applied for proton beam therapy (PBT) to be listed on the Medicare Benefits Schedule (MBS) for the treatment of specific rare cancers in paediatric (children), adolescent, young adult, and adult patients.  Photon radiation therapy (PRT) using X-rays has long been used to treat cancerous and noncancerous (benign) tumours. PBT is a newer type of radiation therapy that uses energy from positively charged particles called protons.  Studies have suggested that PBT may cause fewer side effects than traditional PRT, because doctors can better focus where the proton beams deposit their energy into the tumour tissue and so cause less damage to the nearby healthy tissue.  PBT is not currently available is Australia, however the first Australian PBT centre currently being built in South Australia is expected to commence operation in 2024.  **MSAC’s advice to the Commonwealth Minister for Health**  MSAC supported the creation of new MBS items for PBT for specific rare cancers in paediatric, adolescent, young adult, and adult populations. However, there are several arrangements that need be put in place before the supported MBS listing, to ensure that eligible Australian patients will have equal access to this new technology. This includes setting up a way to collect relevant treatment and outcomes data on Australian patients treated with PRT (before PBT becomes available in Australia) and with PBT (after PBT becomes available in Australia). |

# Summary of consideration and rationale for MSAC’s advice

MSAC recalled that, at its 74th meeting (22-23 November 2018), it had considered a previous application for PBT for the types of patients currently supported under the Medical Treatment Overseas Program (MTOP) ([MSAC Application 1455 - Public Summary Document [PSD]](http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1455-public)). MSAC noted that the current application for PBT (MSAC 1638) intended to address the issues MSAC had previously raised regarding PBT by providing updated evidence of comparative efficacy and safety, a cost-utility analysis, and proposals to address concerns regarding the implementation of an MBS listing.

MSAC noted that the populations proposed in MSAC Application 1638 differed from MSAC Application 1455 and were anatomical-based instead of being tumour-based as recommended by MSAC previously ([MSAC 1455 PSD](http://wcmprd01.central.health/internet/msac/publishing.nsf/Content/1455-public)). MSAC acknowledged there is a clinical need for PBT in patients with rare malignancies in which radiation therapy is the only option, as PBT may reduce the radiation risk to surrounding structures (eg spinal cord) or may reduce the risk of late sequelae in children. Given this, and consistent with its previous advice which reflected the types of patients currently supported under the MTOP, MSAC recommended that PBT be restricted to patients with specific malignancies as follows:

* For an adult patient with:
  + a tumour of the base of the skull, including meningioma, chordoma or chondrosarcoma; or
  + a tumour of the vertebral column or bony pelvis; or
  + an adenoid cystic carcinoma of the salivary or lacrimal gland.
* For a patient under the age of 25 years:
  + with a solid tumour located in:
    - the central nervous system; or
    - the orbit, including retinoblastoma; or
    - the axial skeleton or in close proximity to the axial skeleton, including bone or soft tissue sarcoma; or
  + with one of the following tumour types:
    - craniopharyngioma
    - intracranial germ cell tumour
    - neuroblastoma
    - nephroblastoma.

MSAC noted the pre-MSAC response expressed the applicant’s willingness to work with the Department to amend the item descriptor to specify cancer types and made no change to the expected size of the eligible population. Accordingly, MSAC advised that the proposed item descriptors should be amended to specify the MSAC-recommended patient populations. MSAC also considered the definition for AYA and recommended that the cut-off should be 25 years of age, to be consistent with the definition of AYA in clinical practice and organisations such as Cancer Institute NSW, Cancer Australia. MSAC also supported the Department’s proposal that PBT would be delivered mostly as a Type C procedure.

MSAC recalled that it had previously accepted that PBT “has likely similar effectiveness to PRT overall, but evidence of superior safety over PRT exists only in paediatric tumours, with the most persuasive case being for paediatric brain or spinal tumours, and possibly a subset of adult brain or spinal tumours”. MSAC noted the updated clinical evidence base and acknowledged the limitations in the evidence as highlighted by the Evaluation Sub-Committee (ESC) (e.g. retrospective studies with a high to very high risk of bias in small heterogeneous populations). However, MSAC noted that there was no new evidence to justify changing the previous conclusions on the comparative safety and efficacy of PBT. Therefore, MSAC accepted that PBT has superior safety and non-inferior effectiveness compared with PRT in specified rare cancers in paediatric, AYA, and adult populations who have a demonstrated high clinical need. MSAC advised that, for PBT to be considered for MBS listing in other rare tumour types meeting the biologically plausible intent of the applicant’s anatomical-based item descriptors (beyond those specified by MSAC above), a clear clinical evidence base, with associated economic analysis, would be required for these additional tumour types. MSAC further advised that a stronger clinical evidence base and economic analysis would be required for more common cancer types, noting that current randomised trials which have been conducted in some of these common cancer types (such as non-small cell lung cancer and cancer of the oesophagus) have not convincingly demonstrated any clinical superiority for PBT over PRT.

MSAC noted the economic evaluation was a cost-utility analysis comparing PBT and PRT based upon the proposed cost of PBT (excluding capital costs) of around $43,000 per course versus around $14,000 for PRT. MSAC noted that in comparison, the Australian Government cost is around $284,000 per patient for treatment with PBT overseas under MTOP. From 2015–16 to 2019–20, MTOP has funded approximately seven applicants per year, at a cost of around $2 million per year. MSAC considered that the estimates of cost-effectiveness were uncertain due to limitations in the evidence as highlighted by ESC. However, MSAC accepted that, by sufficiently decreasing the rates of toxicity events across these patients, PBT would result in sufficient net improvements in quality of life and cost offsets from reduced provision of healthcare resources to be acceptably cost-effective overall in the MSAC-supported rare cancer types.

MSAC noted the applicant and relevant specialist organisations supported the proposal to prospectively collect Australian PRT and PBT patient data by extending the type of data collected and collating this at the national level by overlapping within existing arrangements and thus creating the potential to link with similar arrangements established in other countries. MSAC noted the advantage of prospectively collecting Australian data on the differential rates of the applicant-specified toxicity event types that drive the claimed clinical safety advantages and economic cost offsets of PBT against PRT and thus help to verify the rates of these events as inputs into the modelled economic evaluation. MSAC supported data collection on patients treated with PRT (starting as soon as possible and enrolling patients until PBT becomes available through the Australian Bragg centre, this period expected to be from 2021 to 2024) and then collection of the same types of data from patients treated with PBT once the Bragg Centre starts treating patients (expected to be in 2024). However, MSAC noted that more clarity is needed regarding how the Department and relevant stakeholders will establish national data collection on a cohort of patients treated with PRT and a subsequent cohort of patients treated with PBT and that this will require consultation with the applicant and registry owners to establish appropriate data collection and analysis. After considering the Department’s paper on options for data collection, MSAC advised that these detailed proposals should be used as a basis for defining the data to be collected through this MSAC-supported proposal.

MSAC also supported the Department’s proposal that a mandatory comparison of a PRT plan (by the referring centre) and a PBT plan (by the PBT centre) be required for each patient referred for PBT to confirm that PRT would be suboptimal/not appropriate, and thereby confirm the patient’s eligibility for MBS-funded PBT treatment. MSAC noted that infrastructure to compare these plans is already available at the Royal Adelaide Hospital and that the comparison of plans would result in an additional cost to the MBS of $3,417.35 per patient (if confirmed eligible for PBT) or $7,630.58 per patient (if the comparison of plans demonstrate PRT is the preferred therapy). MSAC also acknowledged that its support for this proposal would increase costs in both the cost-utility analysis and the budget analysis, but advised that these consequences were acceptable in the context of its overall support for MBS-funded PBT. MSAC also advised that further efficiencies of about 50% could be gained for this comparison if the same four-dimensional CT is used to develop both the PRT and the PBT plans.

MSAC noted a number of issues regarding implementation that the Department would need to resolve to ensure that the service is implemented nationally in an equitable way to the eligible population. MSAC raised concerns regarding the impact that out-of-pocket costs for travel and accommodation may have on equitable access for patients across Australia. In this regard, MSAC suggested that relevant annual incidence data across each state and territory from the Australian Institute of Health and Welfare (AIHW) or other authoritative data source be collated. MSAC also suggested that the proposed data collection before 2024 could complement this by including the potential numbers of patients who might be referred each year from each centre outside South Australia, and the likely willingness of such referred patients outside Adelaide (and their families as appropriate) to travel to and stay in Adelaide to receive PBT. MSAC supported the Department’s expectation that patients should be bulk-billed for the delivery of its PBT services to ensure equitable access and patient affordability. However, MSAC noted that the eligible patient population could be higher than the Bragg Centre’s operational capacity, and it was unclear how the other associated costs of patient access would be managed or how this would be adapted if additional PBT facilities are established elsewhere in Australia in the future. Therefore, MSAC requested the committee be appraised of the Department’s progress on establishing national data collection for cohorts of patients receiving PRT or PBT, comparison of PRT and PBT plans and resolving implementation issues to ensure equitable access to PBT at MSAC’s 81st meeting (31 March/1 April 2021) before PBT is listed on the MBS.

The MSAC-supported MBS items were as follows, noting that further amendments would be needed to the proposed items and to MBS item 15565 (the existing planning item for PRT) to implement the MSAC-supported proposal from the Department to also require a comparison of PRT and PBT plans for each patient referred for PBT to confirm their eligibility.

| Category 3 – Group T2 – Radiation Oncology |
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| Item 15XXX  Megavoltage Level 6 - Proton Beam Therapy Simulation & Planning for an adult patient with:   * A tumour of the base of the skull, including meningioma, chordoma or chondrosarcoma; or * A tumour of the vertebral column or bony pelvis; or * An adenoid cystic carcinoma of the salivary or lacrimal gland.  1. Simulation for PROTON BEAM THERAPY (PBT), if: 2. Patient set-up and immobilisation techniques are suitable for reliable image volume data acquisition and reproducible PBT treatment; and 3. A high-quality three dimensional or four-dimensional image volume dataset is acquired in treatment position for the relevant region of interest to be planned, treated and verified (through daily planar or volumetric image guidance strategies); and 4. The image set must be suitable for fusion or co-registration with diagnostic quality datasets and generation of quality digitally reconstructed radiographic images to PBT treatment strategies, and 5. Dosimetry for proton beam therapy if: 6. The PBT delivery planning process is required to calculate dose to single or multiple target structures and requires a dose-volume histogram to complete the planning process; and 7. The PBT delivery planning process maximises the differential between target dose, organs at risk and normal tissue dose, based on review and assessment by a radiation oncologist; and 8. All gross tumour volume, clinical target volumes, and organs at risk must be rendered; and 9. Organs at risk must be nominated as planning dose goals or constraints; and 10. Dose calculations and dose-volume histograms must be generated in an inverse planned process, using a specialised calculation algorithm, with prescription and plan details approved and recorded with the plan; and 11. Three dimensional image volume dataset must be used for the relevant region to be planned, treated and verified; and 12. Relevant multimodality diagnostic imaging (including four-dimensional CT, contrast-enhanced CT, magnetic resonance imaging or positron emission tomography), where available, is used to delineate all relevant targets and organs at risk; and 13. Images are suitable for generation of quality digitally reconstructed radiographic images; and 14. The final dosimetry plan is validated by both the appropriately qualified radiation therapist and/or medical physicist, using robust quality assurance processes, with the plan approved by the radiation oncologist prior to delivery, which must include: 15. Determination of accuracy of dose fluence delivered by the pencil beam scanning system and gantry position (static or dynamic); or 16. Ensuring the plan is deliverable, data transfer is acceptable and validation checks are completed on a proton therapy system; or 17. Validation of accuracy of the derived PBT treatment plan; and 18. Comparative proton and photon treatment plans have demonstrated that the patient is at risk of clinically significant side effects if photon radiation therapy were used instead of PBT; and 19. Only three ADDITIONAL dosimetry plans (for re-planning/adaptive strategy) are payable through the MBS during the treatment course (at 50% of the fee for this item), when treatment adjustments are inadequate to satisfy treatment protocol requirements. |
| Fee: $7,630.50 85% Benefit: $7,545.90 |

| Category 3 – Group T2 – Radiation Oncology |
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| Item 15YYY  Megavoltage Level 6 - Proton Beam Therapy Simulation & Planning for a patient under the age of 25 years with a solid tumour located in:   * The central nervous system; or * The orbit, including retinoblastoma; or * The axial skeleton or in close proximity to the axial skeleton, including bone or soft tissue sarcoma;   Or with one of the following tumour types:   * Craniopharyngioma * Intracranial germ cell tumour * Neuroblastoma * Nephroblastoma  1. Simulation for PROTON BEAM THERAPY (PBT), if: 2. Patient set-up and immobilisation techniques are suitable for reliable image volume data acquisition and reproducible PBT treatment; and 3. A high-quality three dimensional or four-dimensional image volume dataset is acquired in treatment position for the relevant region of interest to be planned, treated and verified (through daily planar or volumetric image guidance strategies); and 4. The image set must be suitable for fusion or co-registration with diagnostic quality datasets and generation of quality digitally reconstructed radiographic images to PBT treatment strategies, and 5. Dosimetry for proton beam therapy if: 6. The PBT delivery planning process is required to calculate dose to single or multiple target structures and requires a dose-volume histogram to complete the planning process; and 7. The PBT delivery planning process maximises the differential between target dose, organs at risk and normal tissue dose, based on review and assessment by a radiation oncologist; and 8. All gross tumour volume, clinical target volumes, and organs at risk must be rendered; and 9. Organs at risk must be nominated as planning dose goals or constraints; and 10. Dose calculations and dose-volume histograms must be generated in an inverse planned process, using a specialised calculation algorithm, with prescription and plan details approved and recorded with the plan; and 11. Three dimensional image volume dataset must be used for the relevant region to be planned, treated and verified; and 12. Relevant multimodality diagnostic imaging (including four-dimensional CT, contrast-enhanced CT, magnetic resonance imaging or positron emission tomography), where available, is used to delineate all relevant targets and organs at risk; and 13. Images are suitable for generation of quality digitally reconstructed radiographic images; and 14. The final dosimetry plan is validated by both the appropriately qualified radiation therapist and/or medical physicist, using robust quality assurance processes, with the plan approved by the radiation oncologist prior to delivery, which must include: 15. Determination of accuracy of dose fluence delivered by the pencil beam scanning system and gantry position (static or dynamic); or 16. Ensuring the plan is deliverable, data transfer is acceptable and validation checks are completed on a proton therapy system; or 17. Validation of accuracy of the derived PBT treatment plan; and 18. Comparative proton and photon treatment plans have demonstrated that the patient is as risk of clinically significant side effects if photon radiation therapy were used instead of PBT; and 19. Only three ADDITIONAL dosimetry plans (for re-planning/adaptive strategy) are payable through the MBS during the treatment course (at 50% of the fee for this item), when treatment adjustments are inadequate to satisfy treatment protocol requirements. |
| Fee: $7,630.50 85% Benefit: $7,545.90 |

| Category 3 – Group T2 – Radiation Oncology |
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| Item 15ZZZ  Megavoltage Level 6 – Proton Beam Therapy Treatment & Verification, for an adult patient with:   * A tumour of the base of the skull, including meningioma, chordoma or chondrosarcoma; or * A tumour of the vertebral column or bony pelvis; or * An adenoid cystic carcinoma of the salivary or lacrimal gland.   Proton beam therapy and verification using a device approved by the Therapeutic Goods Administration if:   1. Image-guided proton therapy imaging is used (with motion management functionality if required) to implement a PBT treatment, prepared in accordance with item 15XXX; and 2. PBT delivery mode is utilised (delivered by a fixed or dynamic gantry proton therapy delivery system); and image decisions and actions are documented in the patient’s record; and 3. Payable once only for each attendance at which treatment is given (with two attendances only paid if another site is located in a different organ/part of the body and requires treatment on the same day), and 4. Daily treatment verification is included in the MBS fee, and patient specific PBT quality assurance applied to all cases, with three ADDITIONAL PBT plan/adaptive strategies payable (at 50% of the fee for item 15XXX) when treatment adjustments are inadequate to satisfy treatment protocol requirements. |
| Fee: $800.40 85% Benefit: $715.70 |

| Category 3 – Group T2 – Radiation Oncology |
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| Item 15AAA  Megavoltage Level 6 – Proton Beam Therapy Treatment & Verification, Treatment Strategies for a patient under the age of 25 years with a solid tumour located in:   * The central nervous system; or * The orbit, including retinoblastoma; or * The axial skeleton or in close proximity to the axial skeleton, including bone or soft tissue sarcoma;   Or with one of the following tumour types:   * Craniopharyngioma * Intracranial germ cell tumour * Neuroblastoma * Nephroblastoma   Proton beam therapy and verification using a device approved by the Therapeutic Goods Administration if:   1. Image-guided proton therapy imaging is used (with motion management functionality if required) to implement a PBT treatment, prepared in accordance with item 15YYY; and 2. PBT delivery mode is utilised (delivered by a fixed or dynamic gantry proton therapy delivery system); and image decisions and actions are documented in the patient’s record; and 3. Payable once only for each attendance at which treatment is given (with two attendances only paid if another site is located in a different organ/part of the body and requires treatment on the same day), and 4. Daily treatment verification is included in the MBS fee, and patient specific PBT quality assurance applied to all cases, with three ADDITIONAL PBT plan/adaptive strategies payable (at 50% of the fee for item 15YYY) when treatment adjustments are inadequate to satisfy treatment protocol requirements. |
| Fee: $800.40 85% Benefit: $715.70 |

| In items 15XXX and 15YYY: Proton Beam Therapy is localised through 3D or 4D volumetric imaging to identify Clinical Targets, Organs at Risk and Normal Tissue (and tumour/OAR excursion in the case of 4D applications). Planning includes optimisation of the dose based on assessment of OAR doses. This technique involves very sharp dose gradients adjacent to both targets and organs at risk increasing the consequences of any geometric uncertainty, making daily treatment verification (IGRT) an essential component of quality PBT. In the case of 4D applications, treatment delivery utilises some form of motion management (gating, deep inspiration breath hold, rescanning etc.) and further complicates the planning, delivery and quality assurance processes. It is the tumour location, size, adjacent organs and dosimetry that define the appropriate role for PBT, and support an approach where the clinical circumstances rather than specific diagnoses are the most important determinants for using PBT. Patient specific pre-treatment Quality Assurance will be required and consideration for re-planning/adaption is included.  Delivery Technologies: Proton accelerator based fixed beam PBT, Proton accelerator based PBT with a gantry.  Eligible patients are at risk of clinically significant side effects using other forms of radiation therapy as demonstrated by comparative proton and photon treatment plans.  Grouped Elements: 3D or 4D Simulation/PBT Planning. Daily Verification, Pre-Treatment QA and 3 x Re-planning/Adaption events. |
| --- |

# Background

This is the first submission (Applicant Developed Assessment Report [ADAR]) for MSAC Application 1638 - PBT for paediatric and rare cancers.

PBT is currently not available as a treatment modality in Australia, however PBT treatments at overseas facilities have been accessed by Australian patients with certain cancer types by applying for funding through the MTOP.

MSAC has previously considered an application for PBT, MSAC Application 1455 for PBT for patients supported under the MTOP. At its November 2019 meeting, after considering the strength of available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness in comparison with existing radiation treatments or other options, MSAC did not support funding of PBT for all indications ([MSAC Application 1455 Public Summary Document](http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1455-public) [PSD]).

The ADAR asserted that MSAC Application 1638 was built on MSAC Application 1455, in that it used a ‘modified version’ of the ratified PICO[[1]](#footnote-1) Confirmation for MSAC application 1455 and attempted to address MSAC’s concerns for MSAC Application 1455 by:

* presenting a proposal for new MBS item numbers aligned with the Oncology Clinical Committee Medicare Benefits Schedule Review
* presenting an updated assessment of the clinical evidence based on clinical claims of non-inferiority in terms of efficacy, and superiority in terms of safety
* presenting cost-utility models for PBT based on a “more completely informed economic evaluation”
* addressing the concerns raised in the MSAC 1455 DCA with regards to implementation of PBT in Australia.

The key modifications to the PICO are summarised in Table 1.

**Table 1 Summary of key modifications to the ratified PICO from MSAC Application 1455 used in MSAC Application 1638**

| **PICO item** | **MSAC 1455** | **MSAC 1638** | **Commentary’s evaluation of the change** |
| --- | --- | --- | --- |
| Population | PICO 1: head and skeleton:   * 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   PICO 2: ocular melanoma  PICO 3:paediatrics and adolescents:   * CNS tumours (including craniopharyngioma, intracranial germ cell tumour, meningioma, gliomas, ependymoma, medulloblastoma) * retinoblastoma * neuroblastoma * bone and soft tissue tumours in children (including osteosarcoma, Ewing sarcoma, rhabdomyosarcoma)   PICO 4: other tumours:   * nephroblastoma * adenoid cystic carcinoma of the lacrimal or salivary glands | PICO 1: adult patients with rare cancers of the head or spine:   * brain tumours * base of skull tumours * chordoma * chondrosarcoma * adenoid cystic carcinoma of the salivary or lacrimal gland   PICO 2: paediatric and AYA patients with a solid tumour located in the head, neck or trunk of the body:   * CNS tumours * retinoblastoma * soft tissue sarcomas in close proximity to the axial skeleton (including rhabdomyosarcomas) * craniopharyngioma * intracranial germ cell tumours * neuroblastoma * nephroblastoma | The original four populations were revised into two populations: adult patients with rare cancers of the head and spine, and paediatric and AYA patients with a solid tumour located in the head, neck or trunk of the body.  *The reclassification of clinical indications is reasonable; no additional indications were added. Ocular melanoma was excluded from Application 1638.* |
| Comparators | Usual standard of care, which may include:   * radiation therapy alternatives, such as IMRT, stereotactic radiation techniques or other external beam therapies, and also brachytherapy, * other treatment options specific to the clinical condition (e.g. surgery, chemotherapy, other devices such as laser therapy for ocular tumours), or * no treatment alternatives. | Usual standard of care, which consists primarily of radiation therapy alternatives, such as IMRT and SRT or other external beam therapies. | “Other treatment options specific to the clinical condition” and “no treatment alternatives” were left out in Application 1638. The applicant argued that, after revising the relevant populations, radiation therapy will almost always form a component of the treatment course, whether used as monotherapy or applied in conjunction with other options (surgery, chemotherapy). The applicant argued that other treatment options (surgery, chemotherapy, brachytherapy) are therefore not relevant comparators anymore, and neither is best supportive (i.e. palliative) care.  *This is appropriate.* |

Source: Adapted from Table 1, p31 of the ADAR and Table 14, 2 of the commentary. *Commentary assessment in italics.*

Table 2 presents a summary of the key issues raised by MSAC for MSAC Application 1455, and how the applicant claimed these were addressed in the ADAR for MSAC Application 1638.

**Table 2 Summary of issues raised for MSAC Application 1455 with an assessment of whether and how these were addressed in the ADAR**

| **Key issues raised in PSD for MSAC Application 1455** | **Applicant’s response** | **Commentary’s evaluation of the response** |
| --- | --- | --- |
| There is no high-level evidence for clinical benefit despite likely dosimetric benefits. | The difficulties associated with generating high-level evidence in paediatric and rare cancer populations has been widely discussed. In the absence of this data, applying the radiation protection principle of As Low As Reasonably Achievable, particularly for the paediatric population is an important consideration for PBT. | *The issue of the lack of high-quality clinical evidence remains in the current assessment as all included studies used retrospective designs and were associated with high risk of bias.* |
| Accept that high-level evidence is unlikely in paediatric cases, but request data from prospective registries (lag time ~10 years) and more data from RCTs. | The Royal Adelaide Hospital, a key clinical collaborator in the Australian Bragg Centre project, has joined the Massachusetts General Hospital administered paediatric Proton/Photon Consortium Registry network. The Australian Bragg Centre understands the importance of registry data and are pursuing international clinical collaborations for this purpose. | *No additional comments.* |
| An item descriptor has not been specified. Item descriptors will need to be very population specific, and apply only to protons (not other heavy particles). | The Australian Bragg Centre will work with MSAC to define a suitable level of population specificity. It should be noted however, that in many cases the benefits of PBT are more dependent on the anatomical location of the tumour than specific tumour type. On this basis, the item descriptor for PBT in the current application proposes that the treatment should be available to two patient groups:   * adult patients with rare cancer of the head or spine * paediatric and AYA patients with a solid tumour located in the head, neck or trunk of the body.   The ratified PICO populations further present a list of individual cancers which account for the vast majority of eligible tumours; however, it should be noted that this list is not exhaustive. There are many extremely rare cancer subtypes and histologies which would benefit from PBT, but account for a small fraction of expected use. To ensure these patients have access to treatment with PBT, the proposed item descriptor does not specify which individual cancers are eligible but does require patients to be “at risk of clinically significant side effects using other forms of radiation therapy”. As such, the proposed item descriptor aims to strike a balance between ensuring flexibility and room for clinical discretion, whilst ensuring that PBT is not used in patients who are unlikely to benefit substantially from treatment.  The proposed item descriptors are specific to PBT. | *The proposed item descriptor is specific to PBT, but remains non-specific for the cancer types that would be eligible for treatment. The applicant argues this is based on very rare cancer subtypes and histologies which may benefit from PBT, although it was not specified in the item descriptors how the eligibility of these patients would be determined.* |
| Note that an application for a re-irradiation population is likely to happen in future. | Dependent on the outcome of this MSAC submission, patient demand modelling, clinical service planning by the operator and further clinical trial results, a subsequent submission may be considered. | *A separate population for re-treatment/re-irradiation was not considered in the ADAR.* |
| Item descriptor categories could match photon treatment. | This was adopted in the current application, which proposed PBT as a Level 6 complexity external beam treatment modality with many parts of the wording derived from intensity modulated radiotherapy item descriptors. | *No additional comments.* |
| Explore cost implications for state/territory health budgets (travel/accommodation). | Practical and financial learnings regarding patient and family movement across states were obtained from countries with a similar centralized PBT model to Australia such as Sweden, Denmark and the UK. | *The ADAR attempted to quantify the cost implications for state/territory health budgets, in regards to travel and accommodation, however the costing may be underestimated due to the number of people required to travel (paediatric patients will need to travel with families).* |

Source: Table 1, pxi of the commentary. *Commentary in italics.*

# Prerequisites to implementation of any funding advice

The items on the Australian Register of Therapeutic Goods (ARTG) that are relevant to this application are shown in Table 3.

The ADAR stated that an application process has been initiated to apply for the proton therapy system (ProTom Radiance 330) to be used at the Australian Bragg Centre for Proton Therapy and Research to be listed on the ARTG. The Radiance 330 has received 510(k) market approval from the US Food and Drug Administration ([K134052](https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K134052)).

**Table 3 PBT devices included on the ARTG**

| **ARTG no.** | **GMDN** | **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 |
| 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: Table 15, p4 of the commentary.

Abbreviations: ARTG no=Australian Register of Therapeutic Goods Number; GMDN=global medical device nomenclature

PBT is a complex invasive technology with long-term safety implications classified as medium to high risk by the Therapeutic Goods Administration (TGA) (Class IIB). HealthPACT recommended that management of PBT facilities will also require accreditation and credentialing of staff.

# Proposal for public funding

The applicant-proposed MBS item descriptors are shown in Table 4, Table 5 and Table 6.

**Table 4 Proposed MBS item descriptor for simulation and planning**

| Category 3 – Group T2 – Radiation Oncology |
| --- |
| **Item 15XXX**  Megavoltage Level 6 - Proton Beam Therapy Simulation & Planning  (a) Simulation for PROTON BEAM RADIOTHERAPY (PBT), if:   1. patient set-up and immobilisation techniques are suitable for reliable image volume data acquisition and reproducible PBT treatment; and 2. a high-quality three dimensional or four-dimensional image volume dataset is acquired in treatment position for the relevant region of interest to be planned, treated and verified (through daily planar or volumetric image guidance strategies); and 3. the image set must be suitable for fusion or co-registration with diagnostic quality datasets and generation of quality digitally reconstructed radiographic images to PBT treatment strategies, and   (b) Dosimetry for proton beam therapy if:   1. the PBT delivery planning process is required to calculate dose to single or multiple target structures and requires a dose-volume histogram to complete the planning process; and 2. the PBT delivery planning process maximises the differential between target dose, organs at risk and normal tissue dose, based on review and assessment by a radiation oncologist; and 3. all gross tumour volume, clinical target volumes, and organs at risk must be rendered; and 4. organs at risk must be nominated as planning dose goals or constraints; and 5. dose calculations and dose-volume histograms must be generated in an inverse planned process, using a specialised calculation algorithm, with prescription and plan details approved and recorded with the plan; and 6. three dimensional image volume dataset must be used for the relevant region to be planned, treated and verified; and 7. relevant multimodality diagnostic imaging (including four-dimensional CT, contrast-enhanced CT, magnetic resonance imaging or positron emission tomography), where available, is used to delineate all relevant targets and organs at risk; and 8. images are suitable for generation of quality digitally reconstructed radiographic images; and 9. the final dosimetry plan is validated by both the appropriately qualified radiation therapist and/or medical physicist, using robust quality assurance processes, with the plan approved by the radiation oncologist prior to delivery, which must include: 10. determination of accuracy of dose fluence delivered by the pencil beam scanning system and gantry position (static or dynamic); or 11. ensuring the plan is deliverable, data transfer is acceptable and validation checks are completed on a proton therapy system; or 12. validation of accuracy of the derived PBT treatment plan; and 13. only three ADDITIONAL dosimetry plans (for re-planning/adaptive strategy) are payable through the MBS during the treatment course (at 50% of the fee for this item), when treatment adjustments are inadequate to satisfy treatment protocol requirements. |
| Fee: $7,630.58 |

Source: Table 4, p 38 of the ADAR

**Table** **5 Proposed MBS item descriptor for treatment and verification**

| Category 3 – Group T2 – Radiation Oncology |
| --- |
| **Item 15YYY**  Megavoltage Level 6 – Proton Beam Therapy Treatment & Verification, Treatment Strategies  Proton beam therapy and verification, using a device approved by the Therapeutic Goods Administration if:   1. image-guided proton therapy imaging is used (with motion management functionality if required) to implement a PBT treatment, prepared in accordance with item 15XXX; and 2. PBT delivery mode is utilised (delivered by a fixed or dynamic gantry proton therapy delivery system); and image decisions and actions are documented in the patient’s record; and 3. payable once only for each attendance at which treatment is given (with two attendances only paid if another site is located in a different organ/part of the body and requires treatment on the same day), and 4. daily treatment verification is included in the MBS fee, and patient specific PBT quality assurance applied to all cases, with three ADDITIONAL PBT plan/adaptive strategies payable (at 50% of the fee for item 15XXX) when treatment adjustments are inadequate to satisfy treatment protocol requirements. |
| Fee: $800.41 |

Source: Table 5, p 39 of the ADAR

**Table 6 Explanatory notes**

| In items 15XXX and 15YYY: Proton Beam Therapy is localised through 3D or 4D volumetric imaging to identify Clinical Targets, Organs at Risk and Normal Tissue (and tumour/OAR excursion in the case of 4D applications). Planning includes optimisation of the dose based on assessment of OAR doses. This technique involves very sharp dose gradients adjacent to both targets and organs at risk increasing the consequences of any geometric uncertainty, making daily treatment verification (IGRT) an essential component of quality PBT. In the case of 4D applications, treatment delivery utilises some form of motion management (gating, deep inspiration breath hold, rescanning etc.) and further complicates the planning, delivery and quality assurance processes. It is the tumour location, size, adjacent organs and dosimetry that define the appropriate role for PBT, and support an approach where the clinical circumstances rather than specific diagnoses are the most important determinants for using PBT. Patient specific pre-treatment Quality Assurance will be required and consideration for re-planning/adaption is included.  Delivery technologies: Proton accelerator based fixed beam PBT, Proton accelerator based PBT with a gantry  Patients with one of the following indications are eligible for items 15XXX and 15YYY:   * adult patients with rare cancers of the head or spine * paediatric and AYA patients with a solid tumour located in the head, neck or trunk of the body.   Eligible patients are at risk of clinically significant side effects using other forms of radiation therapy.  Grouped Elements: 3D or 4D Simulation/PBT Planning. Daily Verification, Pre-Treatment QA and 3 x Re-planning/Adaption events. |
| --- |

Source: Table 6, p 39 of the ADAR

The commentary noted that the ADAR followed MSAC’s advice that the item descriptors should be modelled on item descriptors for IMRT procedures ([MSAC Application 1455 PSD](http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1455-public)), and also considered the recommendations from the Oncology Clinical Committee ([Report from the Oncology Clinical Committee 2018](https://www1.health.gov.au/internet/main/publishing.nsf/Content/MBSR-closed-consult)) for a two-part payment model and an additional dosimetry plan for re-planning.

The commentary noted that population restrictions were consistent with the proposed patient population, but that these restrictions were specified in the proposed explanatory notes (Table 6) instead of within the proposed item descriptors. There would also be a potential for other patients to become eligible as the proposed explanatory note also states that “eligible patients are at risk of clinically significant side effects using other forms of radiation therapy.”

The ADAR stated that the proposed fees for PBT planning and treatment services were based on a comparison of the costs associated with professional services time, maintaining service contracts for the PBT or PRT equipment, and consumables associated with providing each service. Recognising that PBT is a more complex and resource-intensive procedure, additional costs associated with PBT were added to the current MBS fees for PRT (IMRT) to determine proposed appropriate MBS fees for the PBT planning and treatment services. Appropriately, these proposed fees did not incorporate any cost of the associated capital equipment.

The commentary also noted that the ADAR did not propose a separate MBS item for re-planning. The ADAR instead suggested utilising the planning and verification item to be payable through the MBS during the treatment course at 50% of the initial planning fee, based on the Report from the Oncology Clinical Committee (2018) ([Medicare Benefits Schedule Review Taskforce, 2018](#_ENREF_34)). The ADAR claimed the re-planning item should be payable up to three times for PBT, compared to only one additional dosimetry plan for the IMRT recommended by the Oncology Clinical Committee.

# Summary of public consultation feedback/consumer issues

Consultation feedback was received from five specialist organisations, a cancer registry organisation, a consumer organisation and an individual consumer in support of MBS listing for PBT in adult patients with rare cancers of the neck and spine, and paediatric and AYA patients with solid tumours located in the head, neck of trunk of the body. The responses highlighted a number of benefits for PBT based on the ability of PBT to deliver radiation more precisely to the tumour than conventional radiation treatment, resulting in fewer side effects and less consequential damage to sensitive nearby parts of the body resulting in less damage in the longer term. This was considered especially relevant for children and young adults. Responses noted that while some patients can access PBT overseas through MTOP or independent funding, MBS listing of PBT would allow for fair and equitable access to PBT for the wider patient population across Australia, and allow Australia to progress with international radiation practices. Responses from the specialist organisations and cancer registry organisation strongly advocated for the national coordination and development of infrastructure for PBT, including auditing, standards and a national registry. Issues previously raised in consultation responses for MSAC Application 1455 ([MSAC Application 1455 PSD](http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1455-public)) were reiterated in the consultation feedback for this application. The following additional issues were noted:

* Patient population: one response suggested the proposed MBS patient populations were too narrowly focused on the indications listed in the MTOP. Due to rapid developments occurring in proton radiotherapy, it was suggested that the proposed patient population underrepresents indications where there is emerging evidence of a clear benefit for the patient and that are now being considered for proton radiotherapy.
* Comparator: while the responses agreed that with the comparison of PBT to PRT, it was suggested that the development of PBT hardware and software (including image guidance) is at least one decade behind PRT. As such, it was suggested that this would distort evidence as proton dose distributions applied to patients in previously reported studies have not been optimised in the same way as has been applied to photon therapy.

# Proposed intervention’s place in clinical management

## Description of proposed intervention

The proposed intervention, PBT, is a form of external beam radiotherapy that uses heavier particles (protons) instead of conventional intensity modulated radiotherapy (IMRT) with photons. Compared to photons, protons have a finite range in matter and have a maximal energy deposition immediately prior to this end of range. This allows for more radiation dose within the tumour rather than the surrounding healthy tissues (Paganetti, 2002).

## Description of medical condition(s)

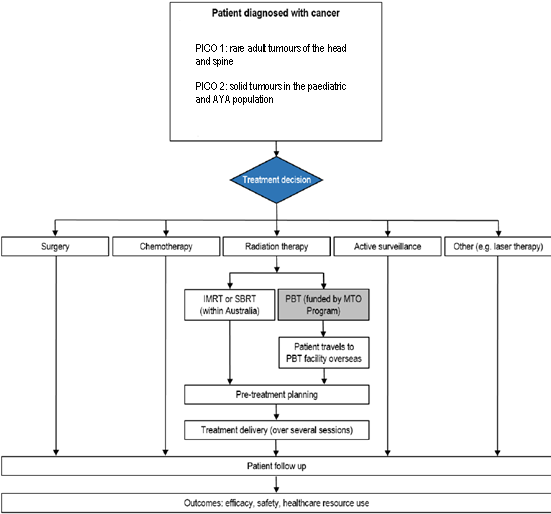
Two patient populations were proposed to be treated with PBT:

* adult patients with rare cancers of the neck and spine, and
* paediatric and AYA patients with solid tumours located in the head, neck or trunk of the body.

The cancers in the two proposed populations were stated to be typically cancers of the central nervous system (CNS) and in proximity to the axial skeleton and would include patients with rare cancers who are currently eligible for funding through MTOP to access PBT overseas.

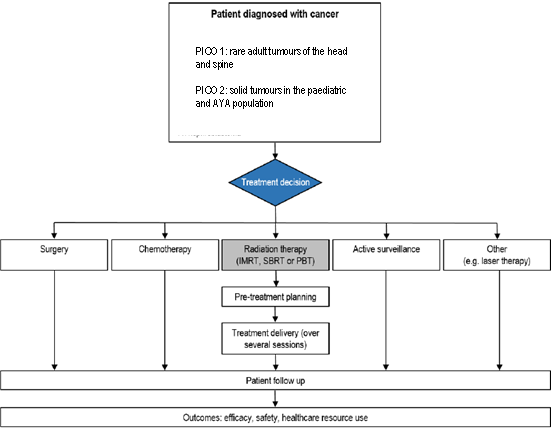
The current and the proposed clinical management algorithms for the treatment of adult patients with rare cancers of the neck and spine (PICO 1), and paediatric and AYA patients with solid tumours located in the head, neck of trunk of the body (PICO 2) are described in Figure 1 and Figure 2, respectively.

The commentary noted that the current and proposed clinical management algorithms are the same algorithms presented in MSAC Application 1455, and are realistic. The addition of the PBT to the current clinical management algorithm would increase the radiation therapy options available in Australia.



**Figure 1 Current clinical management algorithm for PICO 1 and PICO 2**

Source: Figure 2, p 47 of ADAR  
Abbreviations: IMRT=intensity modulated radiation therapy; MTOP=medical treatment overseas program; PBT=proton beam therapy; PICO=population, intervention, comparator, outcome; SRT=stereotactic radiation therapy



**Figure 2 Proposed clinical management algorithm for PICO 1 and PICO 2**

Source: Figure 3, p 48 of ADAR  
Abbreviations: IMRT=intensity modulated radiation therapy; PBT=proton beam therapy; PICO=population, intervention, comparator, outcome; SRT=stereotactic radiation therapy

# Comparator

The proposed comparator, usual standard of care, comprised photon radiation therapy alternatives, such as IMRT, stereotactic radiation therapy (SRT) or other external beam therapies, which were together referred to as PRT. While the clinical assessment included several PRT alternatives funded on the MBS, IMRT was the main PRT comparator.

# Comparative safety

The evidence base presented in the ADAR (MSAC 1638) comprised 28 retrospective comparative studies. In comparison, the previous evidence base presented for MSAC Application 1455 comprised five systematic reviews, two previous health technology assessment reports, and 17 comparative cohort studies (p7, [MSAC Application 1455 PSD](http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1455-public)).

The commentary noted that the literature search conducted in the ADAR was inadequate in identifying all the appropriate available evidence for PBT compared with PRT. Therefore, the commentary conducted a systematic literature search with no date limits and re-evaluated the studies included in the ADAR. The commentary identified four studies that were not included in the ADAR and that 8/28 included in the ADAR (six for the PICO 1 adult population and two for the PICO 2 paediatric and AYA population) did not meet the inclusion criteria as per the PICO. The commentary excluded these eight studies: four for wrong population, three for wrong comparator and one for wrong outcomes. Therefore, the evidence base considered in the commentary included 24 studies.

A summary of the commentary’s evidence bases for PICO 1 and PICO 2 is presented in Table 7 and Table 8, respectively, along with mark-up to show new studies included by the commentary (italics), studies included in the ADAR but excluded by the commentary (~~strikethrough~~) and studies not previously considered as part of MSAC Application 1455 (\*).

For adult patients with tumours of the head and spine (PICO 1), six retrospective comparative studies were included in the commentary evidence base, all six studies were not previously considered by MSAC as part of MSAC Application 1455.

For paediatric and AYA patients with solid tumours (PICO 2), 18 retrospective comparative studies were included in the commentary evidence base, 10 studies were not previously considered by MSAC as part of MSAC Application 1455.

**Table 7 Key features of the included evidence comparing PBT with usual standard of care in adult patients with tumours of the head and spine and assessed to be eligible as part of the independent assessment undertaken for the commentary**

| Trial/Study | N | Design/ duration | Risk of bias | Patient population | Key outcome(s) | *Result used in economic model* |
| --- | --- | --- | --- | --- | --- | --- |
| ~~Kahn 2011\*~~ | ~~32~~ | ~~Retrospective comparative effectiveness~~ | ~~High~~ | ~~Primary intramedullary spinal cord glioma~~ | ~~Local recurrence, OS~~ |  |
| [Brown et al. (2013)](#_ENREF_12)\* | 40 | Retrospective comparative effectiveness  2003-2011 | High | Medulloblastoma | Locoregional failure, weight loss, *acute* toxicities including nausea/vomiting, dermatitis, change in WBC, haemoglobin and platelets,  *PFS, OS* | *Not used* |
| ~~Mima 2014~~ | ~~23~~ | ~~Retrospective comparative effectiveness~~ | ~~High~~ | ~~Chordoma (sacral)~~ | ~~Local tumour control, OS~~ |  |
| ~~Molina 2014~~ | ~~16~~ | ~~Retrospective comparative effectiveness~~  ~~2000-2008~~ | ~~High~~ | ~~Chordomas~~ | ~~OS~~ |  |
| ~~Romesser 2016~~ | ~~23~~ | ~~Retrospective comparative effectiveness~~  ~~2011-2014~~ | ~~High~~ | ~~Major salivary gland cancer or cutaneous squamous cell carcinoma~~ | ~~Acute toxicities~~ |  |
| [Adeberg et al. (2017)](#_ENREF_2)\* | 132 | Retrospective matched comparative effectiveness  *2011-2015* | *High* | High-grade glioma | *Acute* toxicities: Grade 2 and 3 toxicities include intracranial pressure, decreased fine motor skills, seizure, visual deficits, transient hemiparesis, worsened pre-existing symptoms,  *PFS, OS* | *Yes* |
| ~~Gunther 2017~~ | ~~37~~ | ~~Retrospective comparative effectiveness~~  ~~2011-2015~~ | ~~High~~ | ~~Leukaemia/lymphoma with CNS involvement~~ | ~~Acute and long-term toxicities including mucositis, viral and bacterial infections, gastrointestinal toxicity (nausea, vomiting, diarrhoea and bleeding), pulmonary toxicity (pneumonia, cough and pulmonary failure) CNS/neurotoxicity (neuropathy, headache, altered mental status, sensory or motor changes), cardiovascular toxicity (arrhythmia, pericardial fusion, acute hypertension, abnormal ejection fraction, heart failure, ischemic event)~~ |  |
| [Mozes et al. (2017)](#_ENREF_38)\* | 77 | Retrospective comparative effectiveness  2000-2012 | High | Inoperable, residual or recurrent meningioma | *Local tumour control* | *Not used* |
| ~~Bronk 2018~~ | ~~99~~ | ~~Retrospective comparative effectiveness~~  ~~2004-2015~~ | ~~High~~ | ~~Grade II or III oligodendroglioma (n=67) or astrocytoma/glioma (n=32)~~ | ~~Pseudo progression~~ |  |
| [Jhaveri et al. (2018)](#_ENREF_26)\* | 49,575 | Retrospective database comparative effectiveness  2004-2013 | Moderately high | Grade I-IV glioma | *OS* | *Not used* |
| [Alterio et al. (2020)](#_ENREF_6)\* | 44 | Retrospective comparative effectiveness  *2006-2015* | High | Locally advanced nasopharyngeal cancer | *Acute* and late toxicities, PFS, local *tumour* control | *Yes* |
| [*Acharya et al. (2018)*](#_ENREF_1)*\** | *72* | *Retrospective comparative study* | *High* | *Adult cranial gliomas (oligodendrogliomas and astrocytomas)* | *Late radiation-related toxicity* | *Not used* |

Source: Table 19, p21 of the commentary.

Strikethrough indicates that the commentary did not consider the study to be eligible for inclusion: Kahn et al. (2011)– wrong population, Mima et al. (2014)– wrong comparator, Molina et al. (2014)– wrong comparator, Romesser et al. (2016)– wrong population, Gunther et al. (2017)– wrong population, Bronk et al. (2018)– wrong outcomes.

Studies in italics have been identified through the independent search conducted as part of the commentary.

\*New studies not considered in the MSAC application 1455  
Abbreviations: CNS=central nervous system; OS=overall survival; PFS=progression free survival; RT=radiation therapy; WBC=white blood cell count

**Table 8 Key features of the included evidence comparing PBT with usual standard of care in paediatric and AYA patients with solid tumours and assessed to be eligible as part of the independent assessment undertaken for the commentary**

| Trial/Study | N | Design/ duration | Risk of bias | Patient population | Key outcome(s) | *Result used in economic model* |
| --- | --- | --- | --- | --- | --- | --- |
| [Bishop et al. (2014)](#_ENREF_9) | 52 | Retrospective comparative effectiveness  1996-2012 | High | Craniopharyngioma | OS, *disease progression,* safety (*late* RT-related toxicities) | *Yes* |
| [Sethi et al. (2014)](#_ENREF_48) | 86 | Retrospective comparative effectiveness  1986-2011 | High | Retinoblastoma | Safety (rate of in-field or RT-related secondary malignancies) | *Not used* |
| [Song et al. (2014)](#_ENREF_50) | 39 | Prospective comparative effectiveness  2008-2012 | High | *Brain* tumours | Safety (acute radiation-related toxicities) | *Not used* |
| [Yock et al. (2014)](#_ENREF_58) | 120 | Prospective comparative effectiveness  1998-2007 | High | Paediatric CNS tumour | HRQoL | *Not used* |
| ~~Grant 2015\*~~ | ~~86~~ | ~~Retrospective comparative effectiveness~~  ~~1996-2014~~ | ~~High~~ | ~~Retinoblastoma~~ | ~~Incidence of distant metastasis, safety (rate of in-field or RT- related secondary malignancies)~~ |  |
| [Gunther et al. (2015)](#_ENREF_23) | 72 | Retrospective comparative effectiveness  2000-2013 | High | Paediatric CNS tumour (intracranial ependymoma) | Overall survival, *disease-specific survival* | *Not used* |
| [Agarwal et al. (2016)](#_ENREF_3)\* | *39 (47 eyes)* | Retrospective comparative effectiveness  1990-2012 | High | *Retinoblastoma* | Acute toxicities, *late toxicities, enucleation rates, OS, local control* | *Not used* |
| [Eaton et al. (2016a)](#_ENREF_15) | 88 | Prospective comparative effectiveness  2000-2009 | *Moderately* High | Paediatric CNS tumour (medulloblastoma) | OS, *RFS, secondary malignancy, treatment length* | *Yes* |
| [Eaton et al. (2016b)](#_ENREF_16) | 77 | Retrospective comparative effectiveness  2000-2009 | *High* | Paediatric CNS tumour (medulloblastoma) | *Late toxicities (endocrine effects)* | *Yes* |
| [Kahalley et al. (2016)](#_ENREF_28)\* | 150 | Retrospective comparative effectiveness  2002-*2012* | High | Paediatric patients with brain tumours | IQ scores | *Not used* |
| [Kopecky et al. (2017)](#_ENREF_30)\* | 1,277 | Retrospective comparative effectiveness  2004-2009 | High | Medulloblastoma | Survival | *Not used* |
| [Sato et al. (2017)](#_ENREF_47) | 79 | Retrospective comparative effectiveness  2000-2013 | High | Paediatric CNS tumours (ependymomas) | OS, *PFS,* local recurrence *free survival*, safety (*acute and late* RT-related *toxicities*) | *Not used* |
| [Bielamowicz et al. (2018)](#_ENREF_8)\* | 95 | Retrospective comparative effectiveness  1997-2014 | *High* | Medulloblastoma | *Late toxicities (*hypothyroidism) | *Not used* |
| [Paulino et al. (2018)](#_ENREF_43)\* | 84 | Retrospective comparative effectiveness  1997-2013 | High | *Medulloblastoma* | *Late toxicities (*hearing *loss)* | *Yes* |
| ~~Hashimoto 2019\*~~ | ~~17~~ | ~~Retrospective comparative effectiveness~~  ~~2004-2015~~ | ~~High~~ | ~~Medulloblastoma and germ cell tumours~~ | ~~WBC, Haemoglobin level, platelet counts~~ |  |
| [Peterson et al. (2019)](#_ENREF_44)\* | 39 | Retrospective comparative effectiveness  2010-2015 | High | *Paediatric patients with brain tumours* | Working memory, global IQ | *Not used* |
| [Kahalley et al. (2020)](#_ENREF_27)\* | 79 | Longitudinal *retrospective* comparative study  2007-2018 | High | Medulloblastoma | Global IQ, verbal reasoning, perceptual reasoning, working memory, processing speed | *Yes#* |
| [*Gross et al. (2019)*](#_ENREF_21)*\** | *125* | *Retrospective comparative study*  *1998-2017* | *High* | *Brain tumours* | *Neuropsychological outcomes (IQ, attention, memory, visuographic skills, academic skills and parent-reported adaptive functioning* | *Not used* |
| [*Ludmir et al. (2019)*](#_ENREF_31)*\** | *83* | *Retrospective comparative study*  *1998-2017* | *High* | *Low grade glioma* | *Local failure, local control* | *Not used* |
| [*Muroi et al. (2020)*](#_ENREF_39)*\** | *22* | *Retrospective comparative study*  *2011-2017 (proton)*  *1984-2004 (photon)* | *High* | *Diffuse intrinsic pontine glioma* | *OS, PFS* | *Not used* |

Source: Table 20, p23 of the commentary.

Strikethrough indicates that the commentary did not consider the study to be eligible for inclusion: Grant et al. (2015) for wrong population (salivary gland tumours) and Hashimoto et al. (2019) for the wrong population in the comparator arm (most patients aged over 24 years).

Studies in italics have been identified through the independent search conducted as part of the commentary.

\*New studies not considered in the MSAC application 1455

# The reported mean reduction in global IQ was converted into a rate of severe intellectual disability for the cost-utility analysis.  
Abbreviations: CNS=central nervous system; HRQoL=health-related quality of life; IQ=intelligence quotient; OS=overall survival; PFS=progression free survival; RT=radiation therapy; WBC=white blood cell count

## Adult patients with rare cancers of the neck and spine (PICO 1)

Based on the commentary’s defined evidence base, the commentary noted that evidence at high risk of bias was found for improved safety of PBT in terms of acute mucositis and xerostomia and systemic effects (acute bone marrow suppression - anaemia, leukocytopenia and thrombocytopenia; acute nausea/vomiting and acute weight loss). No significant differences in late radiation-related toxicities were found. Few severe acute or late adverse events were reported. Toxicities for which statistical significance was reported are summarised in Table 9.

**Table 9 Summary of statistically significant toxicity data for adult patients with tumours of the head and spine**

| Study ID | Toxicity and grade | PBT  n with event/N (%) | | PRT  n with event/N (%) | Absolute difference  (95% CI) | P-value |
| --- | --- | --- | --- | --- | --- | --- |
| **Acute toxicities** | |  | |  |  |  |
| [Adeberg et al. (2017)](#_ENREF_2) | Grade ≥ 2 toxicity | 6/66 (9) | | 14/66 (22) | -0.12 (-0.24, -0.00) | 0.05 |
| Worsened pre-existing symptoms | 4/66 (8)  *(grade 2: n=3)* | | 11/66 (17)  *(grade 2: n=4,  grade 3: n=3)* | -0.11 (-0.12, 0.00) | 0.05 |
| [Alterio et al. (2020)](#_ENREF_6) | Xerostomia Grade 2 | 2/27 (7) | | 6/17 (35) | -0.28 (-0.51, -0.04) |  |
| Mucositis |  | |  |  |  |
| Grade 1 | 11/27 (40.8) | | 2/17 (11.8) | 0.29 (0.01, 0.57) |  |
| Grade 2 | 13/27 (48.1) | | 2/17 (11.8) | 0.36 (0.08, 0.65) |  |
| Grade 3 | 3/27 (11.1) | | 13/17 (76.4) | -0.65 (-0.95, -0.36) |  |
| **Late toxicities** | |  | |  |  |  |
|  | No significant differences reported | | |  |  |  |
| **Systemic effects** | | |  |  |  |  |
| [Brown et al. (2013)](#_ENREF_12) | *Median (range) % change* in weight at completion of RT | -1.2 (14 to -8.4) | | -5.8 (5.8 to -17.1) | 4.6 | 0.004 |
|  | *Weight loss ≤2%* | *12/19 (63)* | | 3/14 (21) | *0.42 (0.11, 0.72)* | *0.02 comparing weight loss >2%*  *0.004 comparing weight loss >5%* |
|  | >5%-10% | 3/19 (16) | | 8/14 (57) | -0.41 (-0.74, -0.09) | *0.004* |
|  | *Nausea/vomiting* |  | |  |  |  |
|  | *Grade 1* | *10/19 (53)* | | 4/21 (19) | *0.34 (0.06, 0.62)* |  |
|  | Grade 2 | *5/19 (26)* | | 15/21 (71) | *-0.45 (-0.73, -0.17)* | *0.004 comparing grade ≥2* |
|  | Haemoglobin |  | |  |  |  |
|  | Grade 1 (9.5-11 g/dL) | 1/19 (6)  *1/18 (6)* | | 10/20 (48) | -0.45 (-0.73, -0.16)  *-0.44 (-0.69, -0.20)* | *0.04 comparing grade ≥1* |
|  | *Haematologic toxicity 1 month after completing RT* |  | |  |  |  |
|  | *Median (range) % baseline* haemoglobin | 105 (74, 124) | | 88 (68, 106) | 17 | 0.002 |

Source: Table 6, pxix of the commentary  
Italicised text represents additional text in the commentary which was not included in the ADAR  
Abbreviations: CI=confidence interval; MD=mean difference; PBT=proton beam therapy; RD=risk difference; PRT=photon radiation therapy; RT=radiation therapy

**Paediatric and AYA patients with solid tumours located in the head, neck or trunk of the body (PICO 2)**

Based on the commentary evidence base, the commentary noted that PBT had comparable acute and late radiation-related toxicity rates to PRT. For systemic effects, one study noted a lower proportion of grade 3-4 thrombocytopenia in the PBT group (n=7/30; 23%) compared with the PRT group (n=7/13; 54%) in patients with various brain tumours, although there were significant differences in follow-up duration between the two groups. One study looking at medulloblastoma, reported better neurocognitive outcomes in PBT patients compared to PRT patients. The PRT group exhibited a significant decline in global IQ, working memory, and processing speed, whereas the PBT group exhibited stable scores over time in all domains except for processing speed (p=0.003).’ Toxicities for which statistical significance was reported are summarised in Table 10.

**Table 10 Summary of statistically significant toxicity data for the paediatric and AYA population**

| Study ID | Toxicity and grade | PBT  n with event/N (%) | | PRT  n with event/N (%) | Absolute difference  (95% CI) | P-value |
| --- | --- | --- | --- | --- | --- | --- |
| **Acute toxicities** | |  | |  |  |  |
| [Song et al. (2014)](#_ENREF_50) | Diarrhoea *(Grade 1-3)* | 0 | | 3/13 (23) | -0.23 (-0.40, -0.06) | 0.023 |
| **Late toxicities** | |  | |  |  |  |
|  | No significant differences reported | | |  |  |  |
| **Systemic effects** | |  | |  |  |  |
| [Song et al. (2014)](#_ENREF_50) | Thrombocytopenia (grade 3-4) | 7/30 (23.3) | | 7/13 (54) | -0.31 (-0.61, 0.00) | 0.012 |
|  | Haematological parameters change from before CSI to 1 month after treatment mean±SD |  | |  |  |  |
|  | White blood cell count (K/µl) | -0.57±2.22 | | -2.61±2.27 | 2.04 (0.57, 3.51) | 0.009 |
|  | Platelet count\* (x105 cells/µl) | -0.68±0.72 | | -2.74±2.28 | 2.06 (0.79, 3.33) | 0.007 |
| [Eaton et al. (2016b)](#_ENREF_16) | Hypothyroidism | 9/40 (22.5) | | 24/36 (64.9) | OR=0.13 (0.04, 0.41) | <0.001 |
|  | Endocrine replacement therapy | 22/40 (55) | | 29/36 (78.38) | OR=0.30 (0.09, 0.99) | 0.047 |
| **Toxicities specific to each cancer type** | | |  | |  |  |
| [Kahalley et al. (2020)](#_ENREF_27) | Mean global IQ (SE) | 95.7 (4.8) | | 88.1 (5.1) | 7.60 (5.42, 9.78) | 0.009 |
|  | Change in global IQ/year  *Beta* (SE); p-value | 0.3 (0.5); 0.1 | | -0.9 (0.4); 0.009 | 1.20 (1.00, 1.40) | 0.011 |
|  | Perceptual reasoning mean (SE) | 99.8 (5.3) | | 86.0 (5.6) | 13.80 (11.39, 16.21) | p=0.001 (adjusted for covariate: p=0.017) |
|  | Change in perceptual reasoning/year  *Beta* (SE); p-value | 1.0 (0.8); 0.053 | | -0.8 (0.6);.206 | 1.80 (1.48, 2.12) | 0.022 |
|  | Change in working memory/year  *Beta* (SE); p-value | 0.1 (0.7); 0.891 | | -2.2 (0.6); 0.001 | 2.30 (2.01, 2.59) | 0.002 |
| [Gross et al. (2019)](#_ENREF_21) | *Cognitive function domain standardised or scaled score, mean (95% CI)* |  | |  |  |  |
|  | *Full-scale IQ/General Ability Index* | *88.6 (84.0, 93.1)* | | *96.0 (91.8, 100.3)* | *-7.4* | *0.0019* |
|  | *Verbal IQ* | *99.7 (95.3, 104.1)* | | *92.8 (88.4, 97.3)* | *6.9* | *0.033* |
|  | *Performance IQ* | *90.7 (82.5, 98.8)* | | *87.8 (82.0, 98.0)* | *2.9* | *0.03* |
|  | *Digit span* | *8.1 (7.3, 8.8)* | | *7.6 (6.7, 8.4)* | *0.5* | *0.03* |
|  | *Story memory* | *9.5 (8.7, 10.4)* | | *8.7 (7.8, 9.6)* | *0.8* | *0.2* |
|  | *Visual motor integration* | *87.2 (82.9, 91.5)* | | *80.8 (76.7, 85.0)* | *6.4* | *0.035* |
|  | *Word reading/decoding* | *94.1 (89.8, 93.4)* | | *86.4 (81.6, 91.2)* | *7.7* | *0.02* |
|  | *Written calculations* | *90.4 (85.4, 95.4)* | | *83.1 (78.2, 88.0)* | *7.3* | *0.042* |
|  | *Parent-reported general adaptive composite* | *92.0 (87.2, 96.7)* | | *80.7 (76.0, 85.4)* | *11.3* | *0.001* |
|  | *ABAS conceptual domain* | *95.1 (90.7, 99.5)* | | *84.1 (79.1, 89.1)* | *11.0* | *0.001* |
|  | *ABAS social domain* | *95.0 (90.9, 99.2)* | | *86.2 (82.6, 89.8)* | *8.8* | *0.002* |
|  | *ABAS practical domain* | *91.8 (87.1, 96.5)* | | *78.9 (73.2, 84.7)* | *12.9* | *0.0001* |
| **Secondary malignancy** | |  | |  |  |  |
| [Sethi et al. (2014)](#_ENREF_48) | Secondary malignancies | 1/55 (1.8) | | 4/31 (12.9) | -0.11 (-0.21, -0.01) | Sig. |
|  | 10-year cumulative incidence of RT-induced or in-field malignancies (95% CI) | 0% | | 14% (3%-31%) | NE | 0.015 |

Source: Table 7, pxx of the commentary.  
\*Corrected for transfusion

Italicised text represents additional text in the commentary which was not included in the ADAR  
Abbreviations: AYA=adolescent and young adult; ABAS=Adaptive Behaviour Assessment System; CI=confidence interval; CSI=craniospinal irradiation; IQ=intelligence quotient; MD=mean difference; PBT=proton beam therapy; RD=risk difference; PRT=photon radiation therapy; RT=radiation therapy; SE=standard error; SD=standard deviation

Overall, the commentary considered that the safety profile for both populations included in the ADAR was uncertain due to numerous limitations of the studies included in the evidence base. Reported toxicity outcomes differed across studies. This conclusion differs from the previous MSAC assessment of PBT (Application 1455) when MSAC concluded that “evidence of superior safety over photon radiation therapy exists only in paediatric tumours, with the most persuasive case being for paediatric brain or spinal tumours, and possibly a subset of adult brain or spinal tumours.”

The pre-MSAC response acknowledged the limitations in the evidence base, but re-asserted that the majority of studies included reported equal or improved toxicity outcomes with PBT as evaluated against PRT. As such, the applicant asserted the clinical claim of superior safety remained unchanged and was already accepted by MSAC when considering MSAC Application 1455.

# Comparative effectiveness

## Adult patients with rare cancers of the neck and spine (PICO 1)

Based on the commentary evidence base, the commentary stated that the identified evidence suggests possible improved overall survival (OS) for PBT compared to PRT in patients with primary gliomas. No difference in survival (progression-free or OS) between PBT and PRT was found for other conditions. No difference in local tumour control between PBT and PRT was found. No data on other effectiveness outcomes, e.g. mortality, disease progression, incidence of metastases, health-related quality of life (HRQoL) or other patient-relevant outcomes for the PICO 1 population of adult patients with tumours of the head and spine were reported in the ADAR or found in the expanded systematic literature search. Results for the key survival outcomes across the studies are presented in Table 11.

**Table 11 Results of survival outcomes for adult patients with tumours of the head and spine across the studies**

| Study ID | Outcome | PBT n with event/N (%) median (range) | PRT n with event/N (%) median (range) | Absolute difference (95% CI) | P-value |
| --- | --- | --- | --- | --- | --- |
| [Adeberg et al. (2017)](#_ENREF_2) | OS, median (range) | 19.1 months (4-41) | 20.9 months (3-53) | NA | 0.125 |
| PFS, median (range) | 8.8 months (2-32) | 7.2 months (2-39) | NA | 0.4 |
| [Alterio et al. (2020)](#_ENREF_6) | PFS at 2 years | 76% | 69% | NA | 0.4 |
| Local PFS at 2 years | 26/27 (96) *(94)* | 13/16 (81.5) *(89)* | 0.15 (-0.03, 0.33) | NS |
| [Brown et al. (2013)](#_ENREF_12) | OS at 2 years | 94% | 90% |  | NS |
| PFS at 2 years | 94% | 85% |  | NS |
| [Jhaveri et al. (2018)](#_ENREF_26) | OS | 159/170 (93.5)  NR | 45888/49405 (92.9)  *NR* | HRadj=0.66 (0.53, 0.83) | <0.001 |
|  | Propensity matched OS at 5 years | 46.10% | 35.50% | NA | 0.009 |
|  | Propensity-matched median OS | 45.9 months | 29.7 months | NA | NR |

Source: Table 8, pxxiii of the commentary.

Italicised text represents additional text in the commentary which was not included in the ADAR

Abbreviations: HRadj=adjusted hazard ratio; OS=overall survival; NA=not applicable; NS=not significant; NR=not reported; PBT=proton beam therapy; PFS=progression free survival; PRT=photon radiation therapy

**Paediatric and AYA patients with solid tumours located in the head, neck of trunk of the body (PICO 2)**

Based on the commentary evidence base, the commentary stated that the evidence suggests that there is no difference in OS between PBT and PRT. Similar findings were noted for progression-free survival and local tumour control although these were reported by a smaller number of studies. One study reported that paediatric patients treated with PBT had a significantly improved quality of life (QoL) compared to those treated with PRT. Results for the key survival outcomes for paediatric and AYA patients across the studies are presented in Table 12.

**Table 12 Results of survival outcomes for paediatric and AYA patients across the studies**

| **Study ID** | **Outcome** | **PBT** | **PRT** | **adjHR (95% CI)** | **P-value** |
| --- | --- | --- | --- | --- | --- |
| [Bishop et al. (2014)](#_ENREF_9) | OS *at 3 years* | 94.10% | 96.80% | NA | 0.742 |
| [Gunther et al. (2015)](#_ENREF_23) | OS *at 4 years* (95% CI) | 87.5% (51.6, 97.3) | 78.8% (60.6%, 89.3%) | NA | 0.21 |
| [Eaton et al. (2016a)](#_ENREF_15) | OS *at 6 years* (95% CI) | 82% (65.4%, 91.1%) | 87.6% (72.7%, 94.7%) | 2.17 (0.66, 7.16) | 0.201 |
|  | *RFS at 6 years (95% CI)* | *78.8% (63.0%, 89.0%)* | *76.5% (60.6%, 86.6%)* | *1.31 (0.5, 3.41)* | *0.584* |
| [Kopecky et al. (2017)](#_ENREF_30) | OS *at 5 years* | NR | NR | 0.99 (0.41, 2.4) | 0.98 |
| [Sato et al. (2017)](#_ENREF_47) | PFS *at 3 years* (95% CI) | 82% (0.64%, 92%) | 60% (42%, 74%) | NA | 0.0307 |
|  | OS *at 3 years* (95% CI) | 97% (83%, 99%) | 81% (63%, 90%) | NA | 0.08 |
| [*Muroi et al. (2020)*](#_ENREF_39) | *OS, median (range)* | *9 (4-48) months* | *11 (NR) months* | *NA* | *0.16* |
| *PFS, median (range)* | *5 (1-11) months* | *5 (NR) months* | *NA* | *0.169* |

Source: Table 9, pxxiv of the commentary  
Italicised text represents additional text in the commentary which was not included in the ADAR  
Abbreviations: adjHR=adjusted hazard ratio; HR=hazard ratio; NA=not applicable; NR=not reported; OS=overall survival; PBT=proton beam therapy; PFS=progression free survival; PRT=photon radiation therapy; RFS=recurrence free survival

The commentary stated that all results presented in the evidence base should be interpreted with caution given the low quality and a very high risk of bias in the included studies.

## Clinical claim

On the basis of the benefits and harms reported in the ADAR evidence base, the ADAR claimed that, relative to usual standard care, PBT has superior safety and non-inferior effectiveness.

The commentary stated that this clinical claim may not be reasonable based on the evidence base available. In most studies included in the commentary evidence base, for both PICOs, safety of PBT was similar to the proposed comparator. There was some evidence that PBT may lead to better neurocognitive outcomes in the paediatric and AYA population. Similarly, effectiveness did not appear to differ between PBT and conventional radiotherapy modalities with an exception of HRQoL in the paediatric/AYA population, which was reported to be higher for PBT patients in one study.

# Economic evaluation

Based on the clinical claim that PBT has superior safety and non-inferior effectiveness compared to PRT, the ADAR presented a modelled cost-utility analysis (CUA), which is summarised in Table 13.

**Table 13 Summary of the economic evaluation**

| Perspective | Australian healthcare system |
| --- | --- |
| Comparator | Photon radiation therapy |
| Type of economic evaluation | Cost-utility analysis |
| Sources of evidence | Systematic review of comparative toxicity profiles.  QALY losses and costs of each toxicity were limited to the expected duration of the implications of the adverse event. There is a maximum time horizon of a lifetime for those toxicities which are permanent and irreversible.  The life expectancy used in the model was uncertain. |
| Time horizon | 15 years (PICO 1; adult); 75 years (PICO 2; paediatric/AYA) |
| Outcomes | QALYs |
| Methods used to generate results | Expected value analysis: each toxicity was assigned a total cost and total QALY decrement. The total cost and total QALY decrement assigned to each intervention (PRT or PBT) was calculated from the expected frequency of each toxicity reported in the clinical evidence |
| Discount rate | 5% per annum |
| Software packages used | Microsoft Excel |

Source: Table 10, pxxv of the commentary

Abbreviations: PICO=population, intervention, comparator, outcomes; PBT=proton beam therapy; PRT=photon radiation therapy; QALY= quality adjusted life year

The commentary highlighted several limitations of the ADAR’s model:

* The model structure is a simple decision analytic model, which only models rates of toxicities, and the costs and utilities of these toxicities. These key parameters drive the model, however, there is great uncertainty with each of the parameters.
* Most sources of data were not specific to rare cancers, and the applicability of these data to the model is uncertain.
* Annual costs were projected, and discounted, over the estimated life expectancy of the populations: 15 years for PICO 1 (adult) and 75 years for PICO 2 (paediatric/AYA). No evidence was provided in the ADAR to show why these patients would live for these periods, but these estimates were justified in the pre-ESC response.
* The model assumes adverse events occur immediately after PBT or PRT (with the exception of secondary malignancy, xerostomia and mucositis). It is uncertain whether there is a delay to onset of these adverse events and, if so, by how long.
* The cost of endocrine dysfunction was directly calculated by the utilisation of growth hormone therapy, funded on the PBS, and therefore the time on treatment (10 years) was used to determine the overall cost of this toxicity ($23,049.50/year). This cost is a significant driver of the model.
* The rate for endocrine dysfunction for the PICO 1 (adult) population was based on [Appelman-Dijkstra et al. (2011)](#_ENREF_7)[[2]](#footnote-2) which reported a hypopituitarism rate of 66% for patients treated with PRT from which the ADAR estimated a rate of 45% in the PBT arm (by applying relative risk of 0.682 derived from Eaton et al. (2016b)[[3]](#footnote-3)). This estimate in the paediatric population differed to the estimate from Alterio at el. (2020)[[4]](#footnote-4) in the adult population, which reported the endocrine dysfunction rates were 100% in the PRT group and 96.3% in the PBT for any endocrine disorder (MD: -0.04; 95% CI -0.13, 0.06). The difference between these two studies significantly increases the uncertainty of the rate of endocrine dysfunction in the model. As this rate is a significant driver of the model, this uncertainty affects the estimate of overall cost-effectiveness of PBT in both PICO 1 (adult) and PICO 2 (paediatric/AYA) populations.
* The ADAR applied a rate for dysphagia and hearing loss where no statistical significance was reported between the two groups (dysphagia RD: -0.09 [95% CI:   
  -0.32, 0.15]; hearing loss RD: 0.01 [-0.19, 0.20]).
* Utility values used in the model appear to be identified from a systematic review cataloguing EQ-5D scores in chronic disease. Where multiple sources were identified in the systematic review, the ADAR did not discuss why specific utility values were used in the model. Various utility values were not tested in the economic model sensitivity analysis. However, generally, lower disutility values were used in the model reducing the impact on the ICER.
* The ADAR estimated the ratio of PICO 1 (adult) and PICO 2 (paediatric/AYA) patients to be 34.2% and 65.8%, respectively, based on AIHW and ACCR data. These proportions were used to provide an overall weighted ICER reflecting the cost-effectiveness of PBT relative to PRT in the combined PICO populations. Although the commentary considered this approach appropriate, this ratio may vary substantially depending on the definition of eligible adult *vs.* paediatric/AYA cancer types.

The pre-ESC response reiterated that the costs of endocrine replacement therapy and the impact this has in driving the cost-effectiveness of PBT in the ADAR model is consistent with other published studies by Lundkvist et al. (2005)[[5]](#footnote-5) and Mailhot-Vega (2015)[[6]](#footnote-6). The applicant also clarified that that the life expectancy for the PICO 1 (adult) population was based on survival data for patients with meningioma and adenoid cystic carcinoma, and for PICO 2 (paediatric and AYA) population, the survival estimates were based on current Australian life expectancy and the assumption that patients are treated at 10 years of age.

The overall costs and outcomes, and incremental costs and outcomes as calculated for the intervention and comparator in the model, and using the base case assumptions, are shown in Table 14.

**Table 14 Incremental cost-effectiveness of PBT compared with PRT as reported in the ADAR - modified to include the cost of the proposed PRT vs PBT comparison plan**

|  | **Cost** | **Incremental cost** | **Effectiveness (toxicities or QALYs)** | | **Incremental effectiveness** | | **ICER** | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| STEP 1: Cost of radiation treatment per toxicity event avoided | | | | | | | | |
| PICO 1 (adult) |  |  |  | |  | |  | |
| PBT | $43,089  *$46,506* | $29,045  *$32,462* | 0.8380 | | -0.7307 | | $39,748  *$44,426* | |
| PRT | $14,044 |  | 1.5687 | |  | |  | |
| PICO 2 (paediatric/AYA) |  |  |  | |  | |  | |
| PBT | $43,089  *$46,506* | $29,045  *$32,462* | 0.8199 | | -0.6854 | | $42,376  *$47,362* | |
| PRT | $14,044 |  | 1.5053 | |  | |  | |
| STEP 2: Weighted average cost per toxicity event | | | |  | |  | |  |
| PICO 1 (adult) |  |  |  | |  | |  | |
| PBT | $3,265 | -$4,655 | - | | - | | - | |
| PRT | $7,920 |  |  | |  | |  | |
| PICO 2 (paediatric/AYA) |  |  |  | |  | |  | |
| PBT | $71,166 | -$41,798 | - | | - | | - | |
| PRT | $112,964 |  |  | |  | |  | |
| STEP 3: Cost per QALY gained |  |  |  | |  | |  | |
| PICO 1 (adult) |  |  |  | |  | |  | |
| PBT | $46,354  *$49,772* | $24,390  *$27,808* | -0.1398 | | 0.1653 | | $147,539  *$168,209* | |
| PRT | $21,964 |  | -0.3051 | |  | |  | |
| PICO 2 (paediatric/AYA) |  |  |  | |  | |  | |
| PBT | $114,255  *$117,673* | -$12,753  *-$9,335* | -0.3285 | | 0.6503 | | Dominant  *Dominant* | |
| PRT | $127,008 |  | -0.9789 | |  | |  | |
| Combined PICO 1 (34.2%) and PICO 2 (65.8%) | | | | | | | | |
| PBT | $91,050  *$94,467* | -$59.01  *$3,358* | -0.2641 | | 0.4846 | | Dominant  *$6,930* | |
| PRT | $91,109 |  | -0.7486 | |  | |  | |

Source: Table 11, pxxviii of the commentary + *amendments to show the implications for the ICERs of requiring a PRT plan for comparison with a PBT plan by adding $3417.35 per patient for MBS item 15565*.

Abbreviations: AYA=adolescent and young adult; ICER=incremental cost effectiveness ratio; PBT=proton beam therapy; PICO=population, intervention, comparator, outcomes; PRT=photon radiation therapy; QALY=quality adjusted life year

The commentary noted that the relevance of presenting outcomes as a cumulative proportion of toxicities per treatment cost was uncertain as the cost of the actual toxicities was not included in this specific analysis, and the proportions of each toxicities were also uncertain, as there was no consistency in identifying grades of toxicity, or if the toxicity was relevant to the analysis (as defined by statistical significance). Additionally, most toxicity costs used in the ADAR were not specific to the target population, and the time horizon was not adequately justified for each population. Therefore, the weighted average cost per toxicity event was uncertain for each population. Overall, the commentary considered the ADAR reported cost-effectiveness of PBT compared with PRT to be uncertain in the PICO 2 (paediatric/AYA) population and the PICO 1 (adult) population.

The ADAR presented sensitivity analyses on including capital costs, on testing the ICER when excluding extracranial cancers (as these patients have a different toxicity profile to patients with intracranial cancers), along with model duration, discount rate, and the exclusion of each included toxicity (Table 15).

**Table 15 Sensitivity analyses of key model variables**

| Sensitivity analysis | Incremental cost per QALY (incremental cost; incremental QALYs) | | |
| --- | --- | --- | --- |
|  | PICO 1: Adults | PICO 2: Paed/AYA | Both pops |
| Base case | $147,539 ($24,390; 0.165) | DOMINANT (-$12,753; 0.65) | DOMINANT (-$59; 0.485) |
| Include capital costs | $218,704($36,155; 0.165) | DOMINANT (-$988; 0.65) | $24,157 ($11,706; 0.485) |
| Exclude re-planning costs | $90,669 ($14,989; 0.165) | DOMINANT (-$22,154; 0.65) | DOMINANT (-$9,461; 0.485) |
| Exclude extracranial cancers | $105,374 ($22,517; 0.214) | DOMINANT (-$33,774; 0.977) | DOMINANT (-$13,651; 0.704) |
| Exclude: Visual impairment | $175,756 ($26,394; 0.15) | DOMINANT (-$7,137; 0.604) | $9,626 ($4,322; 0.449) |
| Exclude: Xerostomia | $154,538 ($25,268; 0.164) | DOMINANT (-$12,753; 0.65) | $498 ($241; 0.484) |
| Exclude: Endocrine dysfunction | $184,798 ($24,390; 0.132) | $25,123 ($14,485; 0.577) | $42,085 ($17,870; 0.425) |
| Exclude: Dysphagia | $202,937 ($24,390; 0.12) | DOMINANT (-$12,753; 0.65) | DOMINANT (-$59; 0.469) |
| Exclude: Hearing loss | $225,440 ($24,461; 0.109) | DOMINANT (-$12,629; 0.543) | $118 ($46; 0.395) |
| Exclude: Mucositis | $170,300 ($25,924; 0.152) | DOMINANT (-$11,322; 0.637) | $2,987 ($1,407; 0.471) |
| Exclude: Intellectual disability | $147,539 ($24,390; 0.165) | DOMINANT (-$12,753; 0.241) | DOMINANT (-$59; 0.215) |
| Exclude: Secondary malignancies | $154,672 ($24,560; 0.159) | DOMINANT (-$5,362; 0.586) | $11,048 ($4,863; 0.44) |
| Model duration: 5 years | $332,545 ($25,819; 0.078) | DOMINANT (-$7,781; 0.474) | $10,941 ($3,702; 0.338) |
| Model duration: 10 years | $197,305 ($25,018; 0.127) | DOMINANT (-$8,894; 0.513) | $7,072 ($2,696; 0.381) |
| Model duration: 15 years | $147,539 ($24,390; 0.165) | DOMINANT (-$9,766; 0.544) | $4,599 ($1,907; 0.415) |
| Model duration: 20 years | $122,247 ($23,899; 0.195) | DOMINANT (-$10,449; 0.568) | $2,924 ($1,289; 0.441) |
| Discount rate: 0% | $100,072 ($23,299; 0.233) | DOMINANT (-$40,908; 2.186) | DOMINANT (-$18,965; 1.519) |
| Discount rate: 10% | $200,992 ($25,045; 0.125) | DOMINANT (-$2,755; 0.345) | $24,995 ($6,746; 0.27) |

Source: Table 53, p137 of the ADAR

Abbreviations: AYA=adolescent and young adult; PICO=population, intervention, comparator, outcomes; QALY=quality adjusted life year

The commentary noted that the sensitivity analyses reported in the ADAR did not include the costs of toxicities nor the values of utilities included in the model. The commentary considered that there was a high degree of uncertainty regarding the proportional difference in the rates of toxicities, and these rates also need to be tested. Further, some of the rates should be excluded from the analyses as a statistical significance between the two interventions was specifically reported as not being reached. Overall, the ADAR sensitivity analyses did not adequately reduce the parameter uncertainty in the model.

Additional one-way sensitivity analyses were analysed in the commentary, testing the impact of additional numbers of toxicities, varying the rates of toxicity and costs of toxicity on the base case ICER. In all cases, the ICER did not significantly deviate from the base case ICER. However, these sensitivity analyses did not represent the overall impact of endocrine dysfunction in the PICO 2 (paediatric/AYA) population, due to the relatively high (and uncertain) rates of toxicity (55.6% in the PBT arm and 88.2% in the PRT arm) and these additional sensitivity analyses only varied the rates of toxicity by +/-5 events and such a small variation would not significantly impact the overall ICER. Likewise, the total cost per event for endocrine dysfunction in the PRT was 64% higher than the cost per event in the PBT arm. Therefore, further multivariate sensitivity analyses were required to ascertain the impact of these parameters.

The key drivers of the economic model are shown in Table 16. Mucositis (grade 3) in the PICO 1 (adult) population and endocrine dysfunction in the PICO 2 (paediatric/AYA) population constitute the largest proportions of costs attributed to the cost of toxicity for each treatment. This suggests the rate of toxicity and the cost of toxicity for endocrine dysfunction in the PICO 2 (paediatric/AYA) population and the rate of toxicity and cost of toxicity for mucositis (grade 3) in the PICO 1 (adult) population were the key drivers of the model. Additionally, the time horizon in the PICO 2 (paediatric/AYA) population impacts the overall cost of endocrine dysfunction, and therefore is another key driver of the model.

**Table 16 Key drivers of the economic model**

| Description | Method/Value | Impact |
| --- | --- | --- |
| Cost and rate of endocrine dysfunction | PRT (paediatric/AYA): $92,370 [$23,049x10years (discounted @5%) x 51.9%]  PBT (paediatric/AYA): $65,133 [$23,049x10years (discounted @5%) x 36.6%] | Very high; favours intervention |
| Cost and rate of visual impairment | PRT (adult): $2,003 [$5,414x10years (discounted @5%) x 3.57%]  PBT (adult): $0 [$5,414x10years (discounted @5%) x 0%]  PRT (paediatric/AYA): $9,125 [$5,414x75 years (discounted @5%) x 8.65%]  PBT (paediatric/AYA): $3,510 [$5,414x75years (discounted @5%) x 3.33%] | High; favours intervention |
| Cost and rate of mucositis | PRT (adult): $4,149 [$6,597 x 62.89%]  PBT (adult): $2,615 [$6,597 x 39.64%]  PRT (paediatric/AYA): $3,871 [$6,597 x 58.69%]  PBT (paediatric/AYA): $2,441 [$6,597 x 36.99%] | High; favours intervention |
| Time horizon | Adult: 15 years  Paediatric/AYA: 75 years | High; favours intervention |

Source: Table 45, p 95 of the commentary

# Financial/budgetary impacts

An epidemiological approach was used to estimate the financial implications of listing PBT on the MBS for treating adult patients with rare cancers of the neck and spine, and paediatric and AYA patients with solid tumours. The total costs to the MBS resulting from the proposed listing of PBT are summarised in Table 17.

**Table 17 Total costs to the MBS associated with PBT**

|  | **2021** | **2022** | **2023** | **2024** | **2025** |
| --- | --- | --- | --- | --- | --- |
| **PBT** |  |  |  |  |  |
| Number of services | 231 | 353 | 360 | 366 | 372 |
| **Total cost (85% rebate)** | $5,726,862 | $8,743,833 | $8,898,691 | $9,054,742 | $9,211,531 |
| **Costs for PRT *vs* PBT comparison plan (85% rebate) *#*** | *$769,842* | *$1,176,425* | *$1,199,754* | *$1,219,750* | *$1,239,746* |
| **Total cost with costs for PRT *vs* PBT comparison plan (85% rebate) *#*** | *$6,496,704* | *$9,920,258* | *$10,098,445* | *$10,274,492* | *$10,451,277* |

Source: Table 13, pxxxii of the commentary

Italicised text indicates values revised by the commentary to reflect corrected number of services and updated MBS fees

*# These rows show the implications for the financial analyses of requiring a PRT plan for comparison with a PBT plan by adding $3,332.65 per patient for MBS item 15565.*

PBT is expected to be provided on an outpatient basis. Therefore, an 85% rebate was considered relevant to the application. However, the commentary noted that a separate analysis of the financial implications to the safety net was not provided in the ADAR.

The cost per patient of PBT is expected to be $36,857 (at an 85% rebate, corrected for MBS fee update), compared to $12,116 for a course of IMRT (at an 85% rebate, corrected for MBS fee update). The commentary considered this estimate to be reasonable, assuming the utilisation of 30 fractions and 3 replanning assessments per patient were valid.

The ADAR estimated that 231 patients would receive PBT in 2021 and 372 in 2025 (revised estimate). The commentary considered this estimate to be uncertain, as both the number of eligible patients was uncertain, and the expected uptake rates were not justified in the ADAR. The pre-ESC response clarified that eligibility was based on the actual incidence of the most common eligible cancers using data from the Australian Institute of Health and Welfare (AIHW) and the children’s cancer registry. The applicant acknowledged that uptake was less certain, due to a range of factors including referral patterns, willingness and ability to travel and previous treatment history, but claimed that capacity constraints at the proposed PBT facility would ensure that the number of procedures will be less than approximately **redacted** patients per year.

The commentary noted that there was potential for the net cost/year to the MBS to be greater than estimated in the ADAR, as the ADAR expects cost offsets based on adverse events avoided for PBT compared to the conventional radiotherapy, but there was significant uncertainty around the toxicity rates.

# Key issues from ESC for MSAC

| **ESC key issue** | **ESC advice to MSAC** |
| --- | --- |
| Population defined in item descriptors or explanatory note | Defining the eligible population in the item descriptors rather than the explanatory notes would better support compliance measures associated with MBS funding. |
| Proposed population changed from cancer-based definitions to anatomy-based definitions | The proposed population now consists of two broad subpopulations: “adult patients with rare cancers of the head and spine” (Population 1) and “paediatric and adolescent/young adult (AYA) patients with a solid tumour in the head, neck or trunk of the body” (Population 2), rather than disease-specific cancer subtypes. This is inconsistent with MSAC’s previous advice. |
| Adolescent/young adult age definition | Given the broader anatomical eligibility proposed for Population 2, the upper age limit of AYA should be defined as well as whether this would relate to the age at cancer diagnosis, age at PBT initiation, or age at PBT completion. |
| Proposed intervention | The applicant should provide justification for the proposed number of additional dosimetry plans and the fee for the treatment and verification item, and clarification regarding the ‘patient specific PBT quality assurance’. |
| Superior safety | ESC acknowledged the limitations of the overall evidence base, but considered that neither the assessment report nor the commentary provided any new evidence that would substantially challenge MSAC’s previous overarching conclusions of superior safety and non-inferior effectiveness of PBT compared to PRT, although these conclusions might vary by how patients are defined as eligible for the two proposed subpopulations. |
| Uncertainty in the size of safety advantage | The size of safety advantage of PBT over PRT in the two subpopulations remains uncertain based on the total evidence available. This has important implications for the economic evaluation for each subpopulation. |
| Modelling inputs | The rates (and evidence sources) applied in the model for the two subpopulations are uncertain, in particular for the identified key driver of endocrine dysfunction.  Utility values used in the model were derived from a systematic review cataloguing EQ-5D scores in chronic disease that was not included in the clinical evidence base.  The model time horizons reasonably varied across the two subpopulations. |
| Prospective Australian data collection | The ESC supported suggestions for the prospective collection of Australian data to help inform the comparative cost-effectiveness of PBT, including in the event that 5-year interim MBS funding is supported. |

**ESC discussion**

ESC noted the application was requesting MBS listing of PBT for paediatric and rare cancers. ESC noted that MSAC had previously considered an application for PBT (MSAC Application 1455, submitted by a different applicant). At that time MSAC concluded that PBT “has likely similar effectiveness to PRT overall, but evidence of superior safety over PRT exists only in paediatric tumours, with the most persuasive case being for paediatric brain or spinal tumours, and possibly a subset of adult brain or spinal tumours”. MSAC considered that “the economic evaluation did not support a conclusion that PBT would be acceptably cost-effective but would welcome a more completely informed economic evaluation” (see PSD for MSAC Application 1455).

ESC noted that Application 1638 attempted to address the issues previously raised by MSAC by presenting an ADAR that:

* proposed new MBS item descriptors and explanatory notes for PBT,
* provided an updated assessment of the clinical evidence, and
* presented a CUA to estimate the QALY implications of the superior safety profile of PBT over PRT compared with the associated incremental costs.

ESC noted that the proposed eligible populations were defined in the proposed explanatory notes (rather than the proposed MBS item descriptors), and considered that defining the eligible population in the item descriptors would better support compliance measures associated with MBS funding.

ESC noted the two proposed subpopulations had changed from cancer-defined populations to anatomy-defined populations. The PICO populations in Application 1455 referred to disease-specific cancer subtypes, whereas the PICO populations in Application 1638 now comprised two broad population groups: tumours of the head and spine in the adult population (Population 1) and solid tumours in the head, neck or trunk of the body in the paediatric and AYA population (Population 2). ESC noted the pre-ESC response claimed that this approach was “clinically appropriate and more feasible to implement”. However, ESC considered that this approach was inconsistent with MSAC’s advice in the PSD for Application 1455 that “it was important to provide justification for which tumours should be treated with protons rather than conventional modalities of radiation therapy using photons.” This greater degree of imprecision could result in the use of PBT for example, ocular melanoma, which the applicant has accepted not be included in either subpopulation. ESC noted the pre-ESC response from the applicant that emphasised the practical nature of its proposal, and that the likelihood of inappropriate use of PBT would be low due to a “robust national referral network”, but considered that the issue remained for MSAC consideration.

Similarly, ESC considered that it was also unclear whether the applicant was proposing that the text “Eligible patients are at risk of clinically significant side effects using other forms of radiation therapy” as an additional eligibility criterion (narrowing the eligible population) or as an alternative eligibility criterion (widening the eligible population). Further, ESC queried the upper age limit of adolescents and young adults, given that there are different definitions of this age limit in the literature. ESC also questioned whether this age limit would relate to the age at cancer diagnosis, age at PBT initiation, or age at PBT completion.

ESC considered that the proposed number of additional dosimetry plans at 50% of the fee in the proposed simulation and planning MBS item required justification and that the applicant should provide clarification regarding the ‘patient specific PBT quality assurance’ in the proposed treatment and verification MBS item. ESC also considered that the fee for this treatment and verification item needed further justification, particularly in relation to the inclusion of consumables.

ESC reviewed the updated clinical evidence assessment comparing PBT with PRT. Based on the commentary’s advice, this consisted of 28 non-randomised, retrospective comparative studies, although ESC noted the commentary’s view that eight of these studies were inappropriately included and that four additional studies should have been included for a total of 24 new comparative studies. ESC noted that the clinical claim in the ADAR of superior safety and non-inferior effectiveness (for both populations) aligned with MSAC’s previous assessment for PBT (PSD for Application 1455). ESC noted that the commentary’s assessment of the evidence and conclusion of uncertain safety differed from the applicant’s clinical claim and MSAC’s previous assessment of PBT (Application 1455). ESC acknowledged the limitations of the evidence base raised by the commentary, including their inclusion of small heterogeneous populations of inadequate power, their assessment of different cancer types, different outcome measures, different durations of follow-up and different co-administered treatments, and their retrospective study designs with moderate to high risk of bias. However, in the context of the overall clinical evidence available, ESC considered that there was no new evidence that would substantially challenge MSAC’s previous overarching conclusions of superior safety and non-inferior effectiveness of PBT compared to PRT. Rather, ESC considered the key issues were in assessing these conclusions might vary by how patients are defined as eligible for the two proposed subpopulations, and then estimating the size of the safety advantage in the two subpopulations based on the total evidence available. ESC considered that this has important implications for the economic evaluation for each subpopulation.

ESC noted that the applicant submitted a cost-utility analysis comparing PBT and PRT that focused on translating the toxicity profiles into estimates of incremental QALYs gained and associated cost offsets due to reduced use of health care resources to manage these toxicities. ESC noted that the ICER for the paediatric/AYA population (Population 2) was dominant (i.e. more QALYs gained for less cost), whereas the ICER for the adult population (Population 1) was estimated to be $147,539/QALY. A ratio of 34.2% adult patients and 65.8% paediatric/AYA patients was used to determine a weighted ICER for the combined adult and paediatric/AYA population. Using this ratio, the weighted ICER for the combined population was also dominant.

ESC noted that the key drivers of the models were: cost and rate of endocrine dysfunction (for the paediatric/AYA subpopulation); cost and rate of visual impairment; cost and rate of mucositis (for the adult population); and the time horizon of each model. ESC considered that the modelling decision to have different time horizons (15 years for the adult subpopulation and 75 years for the paediatric/AYA subpopulation) was reasonable. ESC noted that the pre-ESC response explained that the adult time horizon was based on life expectancy for patients with meningioma and adenoid cystic carcinoma and that the other time horizon was based on current Australian life expectancy and assuming these patients were treated at 10 years of age on average.

ESC considered that there was uncertainty regarding the appropriateness of the rates applied in the two models and that the base case consistently appeared to favour PBT, in particular for endocrine dysfunction, and to a lesser extent for visual impairment and mucositis. In particular, ESC was concerned that different sources were used to generate rates and rate ratios, and there was an overall disconnect between the evidence presented for the clinical claims and that used in the economic modelling. Further, the ADAR did not present any sensitivity analyses around the costs or utilities used in the model.

ESC noted costs for cognitive impairment or secondary malignancy were not included in the models such that the base case did not favour PBT. Although acknowledging this may have a significant impact, it would be difficult to separate direct and indirect costs if included. In addition, utility values used in the model were derived from a systematic review cataloguing EQ-5D scores in chronic disease that was not included in the clinical evidence base. ESC agreed with the commentary that further multivariate analyses were required to assess the robustness of the economic estimates.

ESC noted an epidemiological approach was used to estimate the financial implications for MBS listing of PBT for the proposed MBS population. ESC noted significant uncertainty in the estimates due to uncertainty in the toxicity assumptions and utilisation uptake rates. Although utilisation was estimated to increase to 372 patients by year 5, ESC noted that the PBT facility could accommodate the treatment of up to **redacted** patients per year.

ESC noted the Department’s proposal for interim MBS items (active for 5 years) to collect Australian data to help inform the cost-effectiveness of PBT. ESC supported the collection of further Australian data to inform a later MSAC reconsideration of PBT, particularly in relation to the types of toxicity which both drive the economic evaluations and would manifest in the time horizon considered reasonable for this data collection. ESC advised that for each type of toxicity, data collection should also include a more robust basis to derive their consequences in terms of utility losses and costs associated with their management, and could consider including other outcomes listed in the PICO. ESC suggested that collecting, analysing and reporting such MSAC-defined data would best be achieved through an existing registry if possible.

ESC noted the supportive consumer input, which highlighted that MBS funding would make this procedure more accessible to more Australians and that PBT delivers radiation more precisely to the affected area, with less damage to nearby healthy body parts and less damage in longer term. However, some patient groups criticised the diagnostic groups listed for the application as being too narrow, and noted that patient and family travel costs might become an issue, especially where inter-state travel is needed.

# Other significant factors

Nil.

# Applicant comments on MSAC’s Public Summary Document

The South Australian Health and Medical Research Institute (SAHMRI) and the Australian Bragg Centre for Proton Therapy and Research (ABCPTR) are pleased with the outcome of the MSAC 1638 application and wish to thank all those involved in the MSAC framework for the thorough review undertaken. The decision reported in this Public Summary Document is of immense importance to those patients diagnosed with a cancer type outlined in the item descriptors and will ensure these patients, where clinically appropriate, are offered equitable access to proton beam therapy (PBT). We look forward to working with the Australian Government Department of Health in establishing a PBT/PRT cancer registry relevant to the MSAC 1638 population to further strengthen the international evidence base for PBT.

# Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website:   
[visit the MSAC website](http://www.msac.gov.au/)

1. Population, Intervention, Comparator, Outcome [↑](#footnote-ref-1)
2. Appelman-Dijkstra, N.M. et al. (2011). J Clin Endocrinol Metab, 96:2330–2340 [↑](#footnote-ref-2)
3. Eaton, B.R. et al. (2016b). Neuro Oncology 18(6), 881–887 [↑](#footnote-ref-3)
4. Alterio, D. et al. (2020). ACTA Oncologica, 59(5): 541–548 [↑](#footnote-ref-4)
5. Lundkvist, J. et al. (2005). American Cancer Society, 103(4):793-801 [↑](#footnote-ref-5)
6. Mailhot-Vega, R. et al (2015). Cancer, 1694-1702 [↑](#footnote-ref-6)