

Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1657 – Rhenium-188 brachytherapy for non-melanoma skin cancer

Applicant: OncoBeta Therapeutics Australia Pty Ltd

Date of MSAC consideration: 27 July 2023

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

1. Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of high-dose brachytherapy with Rhenium-188 (Re-188) for patients with certain keratinocyte cancers was received from OncoBeta Therapeutics Australia Pty Ltd by the Department of Health and Aged Care.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC did not support the public funding of high-dose brachytherapy with an epidermal isotope composed of Re-188 in patients with non-melanoma skin cancers (including basal cell and squamous cell carcinomas) who are contraindicated for surgery.

MSAC considered that the comparative safety and effectiveness of Re-188 relative to external beam radiation therapy (EBRT) was uncertain due to limitations in the evidence base. However, MSAC noted an ongoing prospective study for Re-188 brachytherapy (the EPIC-Skin study) may improve the level of evidence for Re-188 brachytherapy once completed. MSAC considered the economic analysis, which claimed Re-188 brachytherapy was cost-saving compared to EBRT, was highly uncertain. This was primarily due to significant variability in clinical expert advice regarding the appropriate EBRT comparator modalities, weighting of the modalities and fractionation schedules. With respect to the comparator, it was noted that orthovoltage radiation therapy has historically served as the mainstay of treatment for cutaneous malignancy because the maximum beam energy is at the skin surface where the malignancy is located and the radiation dose falls off rapidly, sparing normal tissues. The use of this modality may have reduced because of equipment availability and hence high energy linear accelerator treatment might be utilised in some centres. Because there was lack of clarity around the appropriate EBRT modalities used to treat non-melanoma skin cancers, this created significant uncertainty in the EBRT costs and consequently the claimed cost-savings may not be realised. The financial analysis was also considered to be highly uncertain due to the likely over-estimated comparator EBRT costs and inability to verify and rely on the estimated utilisation of Re-188 brachytherapy.

MSAC advised that should the applicant contemplate a resubmission, any resubmission should present an improved evidence base for the comparative safety (including long-term safety) and effectiveness for Re-188 brachytherapy, provide a more robust estimate of the comparator EBRT cost that is evidence based and considers the different EBRT modalities used (including type of

modalities, weighting and fractionation schedules) to treat the proposed patient population across Australia, revise the economic analysis to address the other issues raised, present a more transparent justification for the estimated utilisation and update the financial analysis accordingly.

Consumer summary

This is an application from OncoBeta Therapeutics Australia Pty Ltd asking for Medicare Benefits Schedule (MBS) listing of Rhenium-188 brachytherapy (Re-188) for non-melanoma skin cancer. Re-188 brachytherapy is a form of radiation therapy where the radioactive source, in this case the Re-188 radioisotope, is placed on the skin to kill the cancer cells. The patient's skin cancer is covered by a protective foil then a physician with a radiation licence applies a paste containing a high-dose of the Re-188 radioisotope onto the foil. The radiation from the Re-188 paste goes through the protective foil and into the skin cancer cells to kill them. The physician determines how long to leave the Re-188 on to achieve the correct radiation dosage to kill the cancer cells. The radiation from Re-188 is not able to penetrate into deep tissue so is only proposed to treat shallow skin cancers (no more than 3mm deep).

Non-melanoma skin cancers are the most common forms of cancer in Australia. Almost 1 million cases are diagnosed and treated each year. At the moment, non-melanoma skin cancers are generally treated with surgery. If a patient is not able to have surgery, then the skin cancer is usually treated with a type of radiation therapy called external beam radiotherapy (EBRT). This is a type of radiation treatment where a machine aims radiation beams at a person's cancer cells to kill them. The radiation dose to kill the skin cancer cells is often delivered in multiple small doses meaning a patient may receive several treatments over a few days to weeks.

The application asked for MBS funding for Re-188 brachytherapy to treat non-melanoma skin cancer patients with lesions on their nose, eyebrow, lip, ear, finger, genitals, shin or collarbone and who are unable to have surgery. That is, RE-188 brachytherapy is not intended to be used instead of surgery, rather RE-188 brachytherapy is intended to be used instead of radiation therapy, such as EBRT when patients cannot have surgery. However, MSAC noted that Re-188 brachytherapy may offer the advantage of being more acceptable to some patients because only one treatment/dose of Re-188 is required. In addition, patients who are not able to tolerate EBRT (eg. due to claustrophobia associated with EBRT machines) may be better suited to Re-188 brachytherapy. However, MSAC noted that further research such as a formal patient preference study (that includes patients who have poorer access to treatments) would be needed to understand how the target patient population are currently treated, patient preferences relative to comparator treatments, what the current access barriers are, and how this may change if Re-188 brachytherapy is listed on the MBS.

After reviewing the evidence, MSAC concluded that there was not enough evidence to be sure that Re-188 brachytherapy gave better patient outcomes than existing radiation therapy, such as EBRT. MSAC noted there is an ongoing clinical trial that includes Australian sites which might improve the level of evidence for Re-188 brachytherapy once completed. MSAC also noted that there are a number of different ways that EBRT can be delivered and this led to difficulties working out how much the EBRT might cost in comparison to Re-188 brachytherapy. MSAC therefore could not be sure that Re-188 brachytherapy would provide better value for money than existing radiation therapy treatment options, including EBRT. MSAC also noted that the doctors who would be able to refer patients for this treatment were dermatologists and plastic surgeons, and their professional associations did not support this application.

MSAC's advice to the Commonwealth Minister for Health and Aged Care

MSAC did not support the application because the clinical comparison of Re-188 brachytherapy with existing radiation therapy is too uncertain at the moment. MSAC was also

Consumer summary
uncertain whether listing Re-188 brachytherapy would result in savings or extra costs to the MBS.

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

MSAC noted that this application from OncoBeta Therapeutics Australia Pty Ltd sought MBS listing of high-dose-rate brachytherapy with Re-188 for the treatment of certain keratinocyte cancers, also known as non-melanoma skin cancers. Specifically, Re-188 brachytherapy was proposed to treat basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (SCC) lesions located on the nose, eyebrow, lip, ear, finger, genitals, shin or collarbone of patients who have comorbidities that prevent surgical excision or patients who have refused such surgery.

MSAC noted the proposed service is a form of brachytherapy treatment that uses an unsealed source of the beta emitter radioisotope Re-188. During treatment, the affected area of the skin is covered with sterile protective foil. A compound paste containing Re-188 is then applied on the foil using a special applicator device. The treatment needs to be performed by a medical specialist with a radiation use licence for using unsealed isotopes, in appropriately accredited facilities. MSAC noted that Re-188 brachytherapy is proposed for use as a single treatment with the duration of treatment calculated to achieve the specific dosage and can be targeted for treatment of locations that might otherwise be difficult to treat using other methods.

MSAC noted the applicant-developed assessment report (ADAR) proposed three MBS items, which differ only in the size of the lesion and the associated fee (Table 2 in Section 6). MSAC noted that the commentary and ESC had raised concerns regarding whether the proposed single fee structure allows for economies of scale in patient treatment, whether the individual cost components such as staff costs had been adequately documented and justified and whether the tiered lesion size approach of the proposed fee structure had properly accounted for batching and wastage costs. MSAC noted that these concerns had not yet been resolved but that the applicant's pre-MSAC response stated willingness to work with MSAC and the department to establish the most appropriate tier structure for the item fees that would encourage efficient delivery of the service using appropriate batching of patients to minimise wastage. MSAC also considered that this item may need to be listed under the "Therapeutic Nuclear Medicine" section of the MBS, as these items have similar requirements (need to be performed in a facility licensed to possess and use unsealed radiation sources, by appropriately trained and experienced specialist medical practitioners who hold a radiation licence for treating people with unsealed sources). MSAC agreed with ESC that any future MBS item descriptor should not be limited to once per lifetime (as a patient may develop skin cancers in other areas in the future), but wording should be included to state that re-treatment of the same lesion is not permitted. Alternative treatments should be sought for non-responders. MSAC noted that the applicant agreed in principle with this approach.

MSAC noted that Re-188 brachytherapy fits into the existing clinical management algorithm as an alternative to existing radiation therapies (EBRT and brachytherapy), and considered this appropriate. MSAC noted that there is a limited clinical need for Re-188 brachytherapy, as a safe and effective treatment (e.g., EBRT) is already available under the MBS for the target population. However, MSAC noted that Re-188 brachytherapy may have some potential advantages over EBRT because it consists of a single treatment (versus multiple visits needed for EBRT), and may be more suitable for claustrophobic patients who are unable to tolerate EBRT machines. MSAC also noted that Re-188 brachytherapy can be provided in nuclear medicine facilities. In contrast EBRT is generally only delivered in hospital departments. This could potentially make Re-188

brachytherapy more accessible than EBRT but this may not be realised in practice as there are currently limited sites providing Re-188 brachytherapy. MSAC also noted that additional sites may be slow to adopt the therapy due to set-up costs. This may mean the treatment may not become widely available unless many patients are to be treated, which could require expanding the eligible population. MSAC noted that further research such as a formal patient preference study (that includes patients who have poorer access to treatments) would be needed to understand how the target patient population are currently treated, patient preferences relative to comparator treatments, what the current access barriers are, and how this may change if Re-188 brachytherapy is listed on the MBS.

MSAC noted consultation feedback from four medical specialist colleges, one consumer organisation and six individual specialist physicians. Three professional colleges were not supportive of the application (Australasian College of Dermatologists [ACD], Australian Society of Plastic Surgeons [ASPS], Royal Australian and New Zealand College of Radiologists [RANZCR]), while two were supportive (Melanoma and Skin Cancer Advocacy Network, Australasian Association of Nuclear Medicine Specialists [AANMS]). The AANMS strongly recommended that this treatment should not be referred to as a brachytherapy, because it involves the use of an unsealed source of radioactivity. MSAC noted that professional bodies representing the proposed referrers for the service specified in the proposed MBS item (dermatologists and plastic surgeons) were not supportive of the application. MSAC noted consultation feedback suggested the availability of Re-188 brachytherapy as an alternative to surgery would provide benefits such as reducing surgery rates and improving cosmetic results in eligible patients. MSAC also noted advice from the RANZCR that in contrast to both modes of EBRT – there was difficulty establishing the dose delivered by R8-188 therapy. MSAC noted the application did not propose that Re-188 brachytherapy would substitute for surgery and that a separate application supported by appropriate comparative evidence for Re-188 brachytherapy versus surgery would be required before this could be considered by MSAC.

MSAC noted the clinical evidence for Re-188 brachytherapy consisted of five (5) published single arm studies, a draft manuscript for another single arm study and an interim report from the EPIC-Skin study¹ (phase IV multicentre-international open label single arm study, N=182). MSAC noted limitations with the Re-188 brachytherapy evidence base included differences in how lesion size were reported (difficult to relate to the proposed MBS items), the inclusion of patients with lesions >8cm² (not applicable to the lesion sizes in the proposed MBS items), the lack of various reported outcomes across the studies and the fact that four of the five studies were from a single centre and risk of bias for the studies was assessed as fair (k=3) to poor (k=2). MSAC noted for the comparison with radiotherapy, which encompassed both EBRT and brachytherapy in the PICO, the ADAR narratively presented 25 EBRT studies. While some of the EBRT studies compared EBRT with other treatment modalities (surgery or brachytherapy), most of the EBRT studies were also single arm studies. MSAC noted that while the ADAR presented its approach as a naïve indirect comparison, the commentary argued (and ESC agreed) that the various studies were too different to facilitate this kind of comparison. MSAC also acknowledged the limitations with the EBRT evidence base which spanned 5 decades, pertained to a mix of different modalities (some of which are outdated) and wider variation in fractionation patterns and provided lack of clarity regarding the indication for the radiation therapy, the lesion size and depth and therefore applicability to the target population. MSAC acknowledged that the formal evidence for EBRT is limited but noted that conventional radiation therapy is a long-standing well-established therapy such that some EBRT MBS items were included on the MBS prior to the establishment of the MSAC health technology assessment process.

¹ Rhenium-Skin Cancer Therapy (SCT) for the Treatment of Non-Melanoma Skin Cancer. (EPIC-Skin) – [NCTC 05135052](#)

Regarding safety, MSAC noted that based on the evidence available, both Re-188 brachytherapy and EBRT appeared to be relatively safe. Rates of relevant adverse events appeared to be similar, although it is difficult to directly compare the different studies. Longer-term safety for Re-188 brachytherapy is uncertain as there is no prospective data available on late toxicity or complications with Re-188 brachytherapy. MSAC noted that the ongoing EPIC-Skin study is expected to end in late 2023 and will provide 24 month follow up data on Re-188 brachytherapy.

MSAC noted another safety issue relates to staff handling of Re-188, as in this form it is an unsealed radiation source and there is a risk of contamination. As such, Re-188 requires standard precautions for handling unsealed sources, including proper personal protective equipment, protective foil to cover untreated skin on the patient, and appropriate containers for radioactive waste. Licensing and accreditation processes are different for sealed and unsealed sources, so facilities administering Re-188 brachytherapy will need appropriate policies, procedures and protective equipment in place.

Regarding clinical effectiveness, MSAC noted the Re-188 brachytherapy studies reported complete response rates similar to that reported in the EBRT studies. MSAC noted although there was no prospective data on cosmesis at later timepoints for Re-188 brachytherapy, the Re-188 brachytherapy studies reported good to excellent early cosmesis outcomes for Re-188 brachytherapy similar to the EBRT studies. MSAC noted the commentary and ESC considered that overall, due to the limitations of the naïve indirect comparison and evidence base, there was insufficient evidence available to evaluate the comparative effectiveness of Re-188 brachytherapy and EBRT for BCC and SCC. MSAC considered that there is some evidence for short-term effectiveness for Re-188 brachytherapy, while the long-term effectiveness is less certain.

Overall, MSAC considered that the comparative effectiveness and safety of Re-188 brachytherapy versus EBRT was uncertain at this time. MSAC noted the final peer-reviewed results from the international EPIC-Skin study may assist with MSAC decision-making regarding the ADAR's clinical claims.

Regarding the economic evaluation, MSAC noted the PICO had specified a cost-effectiveness analysis would be most appropriate. Instead, the ADAR presented a cost-comparison analysis comparing MBS-funded healthcare resources for EBRT with Re-188 brachytherapy. The ADAR justified the cost-comparison approach based on the downgrading of the clinical claim to non-inferior safety and effectiveness, due to the limited availability of data. MSAC noted the key issue with the economics was regarding whether the ADAR had appropriately costed the comparator. MSAC noted the PICO confirmation listed the comparator as radiation therapy (EBRT or brachytherapy) or best supportive care. MSAC noted the economic analysis had only included EBRT and while EBRT is an appropriate comparator, the issue of which modality of EBRT and how many fractions are used to treat the target lesions in Australian clinical practice is highly uncertain due to differing expert opinion. MSAC noted the ADAR costed EBRT based on a mix of 3 modalities: electrons or photons using a linear accelerator (LINAC), intensity modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT). The ADAR costed "LINAC" using MBS items for 3D megavoltage EBRT. MSAC noted ESC advice that 2D rather than 3D electron beam EBRT would be used for treatment of shallow and small ($\leq 3\text{mm}$) BCC or SCC. The commentary and consultation feedback from RANZCR considered that orthovoltage was a more appropriate EBRT modality for treating the target lesions. MSAC noted that 2D electron beam and orthovoltage MBS items are less expensive than 3D megavoltage. Subsequently, MSAC noted that the sensitivity analyses in the commentary and ESC report demonstrate that including these modalities in the EBRT costing make a significant difference to comparative EBRT costings and whether or not Re-188 brachytherapy is cost saving compared to EBRT. MSAC noted the applicant's pre-MSAC response disputed the EBRT modalities, weightings and fraction schedules

proposed by the commentary and ESC. The pre-MSAC response reiterated that the applicant had conducted a targeted clinical consultation process with a panel of experienced Australian radiation oncologists during preparation of the ADAR in order to better understand current local clinical practice in relation to EBRT, and that this panel had not mentioned orthovoltage as an appropriate EBRT modality for the proposed population.

MSAC also noted that the appropriate number of fractions of EBRT was also unclear. The ADAR assumed a fractionation range of 10–30 fractions would be used per lesion, with an average of 19.03 fractions from the 100-sample simulation. MSAC noted the commentary highlighted that a range of 23–47 Gy per lesion was used in one of the Re-188 brachytherapy studies, and according to eviQ guidelines² the fractionation range is 5–20 fractions per lesion for a prescription dose of up to 50 Gy. Further, the standard curative dose schedules for the treatment of small lesions (< 2 cm) typically require fewer treatments (4–12 treatments over 1–2 weeks), compared with larger lesions, which require 15–30 treatments over 3–6 weeks. MSAC noted advice from ESC that generally 5–10 fractions per lesion would be most commonly used.

MSAC considered that, due to the significant variability in clinical expert advice regarding the appropriate EBRT modalities, weighting of the modalities and fractionation schedules, the costings for the comparator were highly uncertain and therefore the ADAR's claim that Re-188 brachytherapy is cost saving compared to EBRT is uncertain and may not be realised. MSAC noted that orthovoltage has historically served as the mainstay of treatment for cutaneous malignancy because the maximum beam energy is at the skin surface where the malignancy is located and the radiation dose falls off rapidly, sparing normal tissues. Although, MSAC noted that the use of orthovoltage may have reduced because of equipment availability and hence high energy linear accelerator treatment might be utilised in some centres. MSAC considered that the appropriate comparator costs could not be resolved at this time due to the conflicting expert advice. MSAC considered that a more robust estimate of the comparator cost that is evidence based and considers the different radiation therapies used to treat the proposed patient population across Australia is required. This estimate should specify the type of EBRT modalities, weighting of the modalities and fraction schedules used and also whether any patients are being treated with contact brachytherapy using a radiation mould (note brachytherapy was included in the PICO but excluded from the ADAR based on the applicant's clinical expert advice). MSAC also considered that, assuming a clinical claim of non-inferior safety and effectiveness is maintained, the applicant would need to present an appropriately revised economic analysis (i.e., a cost-minimisation analysis).

MSAC considered the financial estimates to be very uncertain. MSAC noted the issues raised in the economic analysis regarding the EBRT modality, weighting and fraction schedules also created significant uncertainty in the ADAR's financial analysis. MSAC also noted that the population size was based on expert opinion that could not be verified and that registry data (that includes Australian patients) that may help inform utilisation was not yet available. MSAC considered that a more robust estimate of population size is required. MSAC noted that the ADAR estimated that MBS listing of Re-188 brachytherapy would result in a cost saving of approximately \$35 million over 6 years. However, MSAC noted that sensitivity analyses exploring the uncertainty in the EBRT costing indicate that the claimed cost savings may not be realised depending on the EBRT modalities, weightings and fractionation schedules used. MSAC considered that the financial impact of listing Re-188 brachytherapy on the MBS was highly uncertain at this time.

² eviQ, Skin cancer basal cell carcinoma definitive EBRT, Accessed at: <https://www.eviq.org.au/radiation-oncology/skin/1032-skin-cancer-basal-cell-carcinoma-definitive-e#dose-prescription>.

Overall, MSAC did not support MBS listing of Re-188 brachytherapy as MSAC considered the comparative safety and effectiveness of Re-188 brachytherapy versus EBRT was too uncertain at present. MSAC noted an ongoing prospective study for Re-188 brachytherapy (the EPIC-Skin study) may improve the level of evidence for Re-188 brachytherapy once completed. MSAC also considered the economic and financial analyses were highly uncertain, due to uncertainty in the comparator costings (due to conflicting expert advice regarding the appropriate EBRT modalities, weighting of the modalities and fractionation schedules), and the inability to verify the estimated number of patients in the defined population that would use Re-188 brachytherapy.

MSAC considered that any resubmission would need to include:

- an improved evidence base for the comparative safety (including long-term safety) and effectiveness for Re-188 brachytherapy, e.g., include data from the EPIC-Skin study and any relevant registry data
- a more robust estimate of the comparator EBRT cost that is evidence based and considers the different EBRT modalities used (including type of modalities, weighting and fractionation schedules) to treat the proposed patient population across Australia. This should specify whether orthovoltage or high energy linear accelerator treatment is the standard of care and the rationale for this determination (especially given the cost differential between the modalities)
- a more transparent estimation of the number of individuals in the eligible population and justification for the estimated number of patients that would utilise Re-188 brachytherapy
- any additional research that can be conducted into patient preferences for this treatment relative to comparators
- revised MBS item descriptor(s) with revised approach to fees for varying lesion sizes
- consideration and specification of which health professionals deliver the treatment and how batching of patients can be achieved to minimise wastage
- revised economic and financial analyses.

4. Background

MSAC has not previously considered high dose brachytherapy with Re-188 for patients with certain keratinocyte cancer.

5. Prerequisites to implementation of any funding advice

The Rhenium Skin Cancer Therapy (Rhenium-SCT) system for treating skin cancer using the radioisotope Rhenium-188 is included on the Australian Register of Therapeutic Goods (ARTG) (see Table 1).

Table 1 ARTG entries for Rhenium-SCT

Product name and Sponsor	ARTG summary	Functional description	Intended purpose
Rhenium-SCT® OncoBeta Therapeutics Pty Ltd	<p>ARTG ID: 400142 Start date: 24 November 2022 Category: Medical Devices Class IIb GMDN: 38299 Radionuclide system, therapeutic, brachytherapy, manual</p> <p>ARTG ID: 351390 Start date: 9 December 2020 Category: Medical Device Class IIb GMDN: 38299 Radionuclide system, therapeutic, brachytherapy, manual</p>	High-dose brachytherapy with Rhenium-188	Treating certain keratinocyte skin cancers using the radioisotope Rhenium-188

Source: ARTG website: www.tga.gov.au/resources/artg, accessed 26 April 2023.

Abbreviations: ARTG ID= Australian Register of Therapeutic Goods identification; GMDN= Global Medical Device Nomenclature; SCT= skin cancer therapy; TGA= Therapeutic Goods Administration.

6. Proposal for public funding

The ADAR proposed three new MBS items for high-dose brachytherapy with Re-188 for treatment of cutaneous basal cell carcinoma (BCC) or cutaneous squamous cell carcinoma (SCC) which would be specific to Re-188 brachytherapy, but not necessarily Rhenium-SCT® system (Table 1).

The proposed three-tiered banding structure for the new MBS items is arbitrary, being based on expected differences in the cost of the Re-188 compound by the size of the lesion. These bands are consistent with the ratified PICO confirmation ([MSAC 1657 Ratified PICO Confirmation](#)).

The ADAR proposed to create three new MBS items (Table 2) instead of amending existing brachytherapy MBS items for construction and application of a radioactive mould to an external surface and associated planning/verification services (15536, 15351, 15354, 15357 and 15800). The ADAR claimed that it would not be optimal to include Re-188 brachytherapy within existing MBS items due to fundamental differences in the methods and costs involved in the respective brachytherapy modalities.

Table 2 ADAR proposed MBS item descriptors for high-dose brachytherapy with Rhenium-188 for keratinocyte cancers

Category 3 – Therapeutic Procedures – Group T2 - Radiation Oncology; Subgroup 4 - Brachytherapy
<p>MBS item XXXX₁</p> <p>Epidermal radioisotope therapy, using rhenium-188, of a cutaneous basal cell carcinoma (BCC) or cutaneous squamous cell carcinoma (SCC) if:</p> <ul style="list-style-type: none"> a) malignancy has been confirmed and other diagnoses excluded by histological examination; and b) the maximum depth of the lesion is less than or equal to 3 mm; and c) the area of the lesion is at least 1.5 cm² but no more than 3.0 cm²; and d) the lesion is located on the nose, eyebrow, lip, ear, digit, genitalia, shin or collarbone or a contiguous area; and e) the patient has comorbidities that prevent surgical excision, or has refused surgery; and g) the service is provided by a suitably trained nuclear medicine physician or radiation oncologist in an approved facility; and h) the service is referred to by a specialist dermatologist or plastic surgeon.
Fee: \$3,420.00

Category 3 – Therapeutic Procedures – Group T2 - Radiation Oncology; Subgroup 4 - Brachytherapy
MBS item *XXXX₂
Epidermal radioisotope therapy, using rhenium-188, of a cutaneous basal cell carcinoma (BCC) or cutaneous squamous cell carcinoma (SCC) if: a) malignancy has been confirmed and other diagnoses excluded by histological examination; and b) the maximum depth of the lesion is less than or equal to 3 mm; and c) the area of the lesion is at least 3.1 cm ² but no more than 5.0 cm ² ; and d) the lesion is located on the nose, eyebrow, lip, ear, digit, genitalia, shin or collarbone or a contiguous area; and e) the patient has comorbidities that prevent surgical excision, or has refused surgery; and g) the service is provided by a suitably trained nuclear medicine physician or radiation oncologist in an approved facility; and h) the service is referred by a specialist dermatologist or plastic surgeon.
Fee: \$4,781.00
MBS item *XXXX₃
Epidermal radioisotope therapy, using rhenium-188, of a cutaneous basal cell carcinoma (BCC) or cutaneous squamous cell carcinoma (SCC) if: a) malignancy has been confirmed and other diagnoses excluded by histological examination; and b) the maximum depth of the lesion is less than or equal to 3 mm; and c) the area of the lesion is at least 5.1 cm ² but no more than 8.0 cm ² ; and d) the lesion is located on the nose, eyebrow, lip, ear, digit, genitalia, shin or collarbone or a contiguous area; and e) the patient has comorbidities that prevent surgical excision, or has refused surgery; and g) the service is provided by a suitably trained nuclear medicine physician or radiation oncologist in an approved facility; and h) the service is referred by a specialist dermatologist or plastic surgeon.
Fee: \$6,726.00

Source: Table 1-2, pg 23 of MSAC 1657 ADAR+in-line commentary

Abbreviations: MBS Items XXXX₁, XXXX₂, XXXX₃ are the proposed three new items described by the Applicant.

A breakdown of the cost components for the proposed MBS fees is presented in Table 3. The ADAR proposed MBS fees would include the entire workflow of the nuclear medicine facility from admission of a referred patient with definitive histology and appropriate marking of the treatment area to their discharge into the community, irrespective of the specific arrangements for provision of the service within individual clinics. The ADAR applied the following key assumptions when estimating the costs components for the proposed MBS fees:

- The average transported cost of each Re-188 carpoule is approximately \$14,000.
- Each carpoule contains sufficient compound to treat lesions with total area of approximately 18 cm².
- Capital equipment costs of approximately \$200,000 were amortised over 5 years, with 260 clinic days per year and 8 patients per day.
- Specialist, nursing and technician time of approximately 3 hours per patient in a discrete clinical setting.
- Overhead costs derived for a dedicated privately operated Re-188 brachytherapy clinic treating approximately 8 patients per day.
- Total cost for each tier calculated for the mid-point of the dose range: 2.25, 4.0 and 6.5 cm².
 - That is, the cost of Re-188 carpoule (\$14,000) was divided by 18 to get a cost per cm² which was then multiplied by the mid-point of the dose range. E.g., for lesions 1.5-3.0 cm², the cost of Re-188 was calculated as \$14,000 divided by 18 multiplied by 2.25 which equals \$1,750.

Table 3 Breakdown of estimated costs of high-dose brachytherapy with Rhenium-188

Item	Lesions 1.5-3.0 cm ²	Lesions 3.1-5.0 cm ²	Lesions 5.1-8.0 cm ²
Re-188 compound	\$1,750	\$3,111	\$5,056
General consumables ¹	\$50	\$50	\$50
Specialists ²	\$500	\$500	\$500
Nursing	\$300	\$300	\$300
Technician	\$300	\$300	\$300
Capital depreciation ³	\$20	\$20	\$20
Overheads ⁴	\$500	\$500	\$500
Total	\$3,420	\$4,781	\$6,726

Source: Table 1-1, pg 22 of MSAC 1657 ADAR+in-line commentary

¹ General consumables: foil, gloves, waste containers.

² Clinical input from a multidisciplinary care team: specialists, nurses, technicians.

³ Capital depreciation on the required capital equipment: application system, measurement, and waste stations.

⁴ Attributable overhead costs of the facility: administration, rent, insurance.

The commentary noted the following issues with the proposed MBS items and fees:

- The single fee structure does not allow for economies in scale when treating a patient with multiple lesions.

The three proposed MBS items are each for treating a single lesion (within one of the 3 lesion size ranges). However, some patients may have more than one lesion, but the single MBS fee structure does not allow for economies of scale when treating a single patient with multiple lesions. That is, the proposed items include \$1100 for specialist, nursing and technician time of approximately 3 hours per patient. If a patient had 3 lesions each measuring 8 cm² treated, this could attract the MBS fee three times which would equate to \$3300 in staff time costs to treat a single patient within one episode. This may not be commensurate with the staff time costs for treating a single patient with 3 lesions.

- The ADAR has not addressed batching and wastage.

The cost component for the Re-188 compound in each of the three proposed MBS items is estimated based on the amount of compound required to treat the average lesion size for each of the three proposed items (i.e. for lesions 1.5-3.0 cm² an average lesion size of 2.25 cm² to calculate the \$1,750 Re-188 compound cost component). However, the Re-188 compound is supplied in a carpoule (\$14,000) that contains enough compound to treat 18 cm². The ADAR approach to costing the RE-188 compound component of the MBS fee implies that batching is required (i.e. one carpoule is used to treat multiple patients with a single lesion and/or a patient with multiple lesions). Some wastage may occur which will vary depending on how efficiently lesions are batched. It is unclear if patients would be charged out-of-pocket costs for any wastage. This could be significant (e.g. potentially \$777 per cm² wastage based on \$14,000 for a carpoule that can treat 18 cm²). The ADAR has not addressed the issue of batching or wastage and has not accounted for this in the economic or financial analysis.

- Discrepancy in the area treated by one carpoule (18 cm² vs 25 cm²).

In the ratified PICO confirmation, it is stated that one carpoule of Re-188 filled with approximately 300mg of the Re-188 compound which is sufficient to treat an area of up to 25 cm² (MSAC 1657 Ratified PICO Confirmation, page 20). However, in the ADAR it is stated that each carpoule contains enough compound to treat a lesion area with

approximately 18 cm². This discrepancy in the assumed lesion areas treated by the Re-188 compound should be clarified by the applicant to aid ESC and MSAC decision making.

- Justification for the costs for staff cost components.

The commentary noted that the type of staff cost components in Table 3 align with the clinical workflow for Re-188 brachytherapy treatment depicted in Figure 1. However, the commentary considered that the costs included for specialists, nursing and technician included in Table 3 were not adequately justified in the ADAR. In regard to specialist costs, the ADAR stated that it is assumed that all patients will require one initial specialist consultation with a dermatologist, radiation oncologist or plastic surgeon (MBS Item 104, 100% Schedule Fee: \$91.80) for diagnosis and referral and a subsequent follow up consultation with the same specialist (MBS Item 105, 100% Schedule Fee: \$46.15) to assess the outcome of the treatment. However, there was insufficient information to understand and justify how the estimated \$500 for specialists was derived. Similarly, nursing costs of \$300 and technician costs of \$300 are included but there is no further information justifying how the costs were attributed.

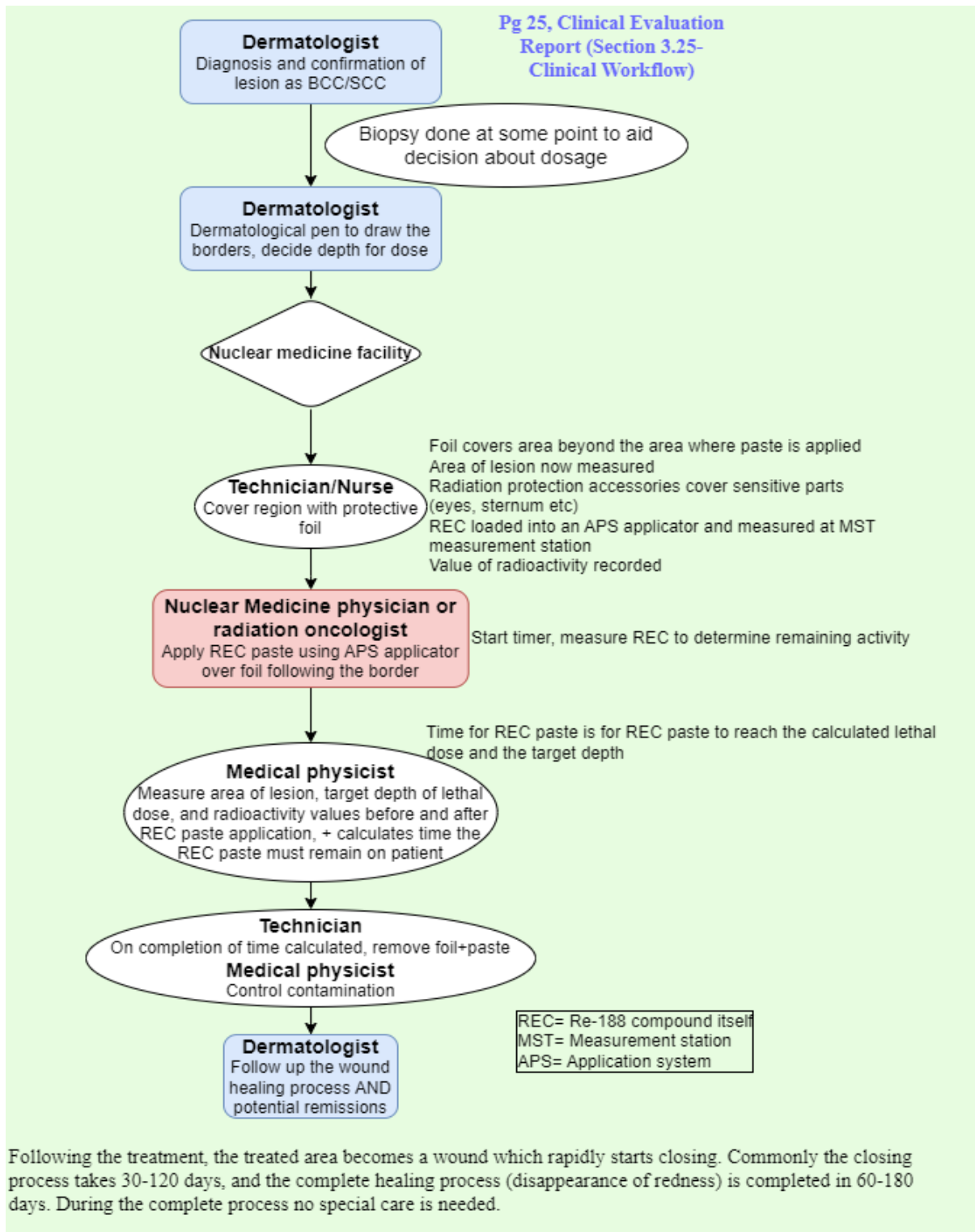


Figure 1 Clinical workflow for treatment of non-melanoma skin cancers with Re-188 brachytherapy

Source: MSAC 1675 ADAR, Attachment - Clinical Evaluation Report

7. Population

The ADAR defined the population as patients with histologically confirmed BCC or SCC, of relatively shallow depth and moderate size (depth ≤ 3 mm and area 1.5-8.0 cm²), located on the

nose, eyebrow, lip, ear, digit, genitalia, shin or collarbone, or a contiguous area, who have comorbidities that would prevent surgical excision, or who otherwise refuse surgery.

The commentary noted the ADAR had expanded the population in the ratified PICO confirmation ([MSAC 1657 Ratified PICO Confirmation](#)) to include patients 'who otherwise refuse surgery'. The clinical assessment of comorbidities that would prevent surgical excision on a case-by-case basis already creates difficulties for defining a PICO and for tightening the proposed MBS descriptor to avoid unintended use outside of the proposed population.

The ADAR also mentioned some rarer lesions. These come under a third group of keratinocyte dysplasia (<1% of keratinocyte cancers) and include some additional conditions that were unclarified: solar keratosis; Bowen's Disease/Bowenoid keratosis a precancerous form of lesion for SCC; Actinic keratoses a precancerous form of lesion for SCC; extramammary Paget's disease.

In current practice, patients with suspected keratinocyte cancer typically present initially to a general practitioner, who, in the majority of cases, surgically excises the lesion or prescribes one of several available topical therapies, with or without concurrent histology. Higher risk lesions, those in a challenging anatomical location, or patients with relevant limiting comorbidities or other objections to surgery, would usually be referred to a dermatologist, radiation oncologist or plastic surgeon, who in many cases would collaborate with a representative of the other speciality within a multidisciplinary care model.

The proposed clinical management algorithm showing the addition of Re-188 brachytherapy as an alternative to other radiotherapy modalities is presented in Figure 2. Note this algorithm does not depict the clinical pathway for patients 'who otherwise refuse surgery' but the commentary considered that this pathway may be similar to the pathway for patients contraindicated to surgery.

At an individual patient level, Re-188 brachytherapy would directly substitute other modalities of radiotherapy, with the two approaches almost never being used consecutively for the same lesion. However, at a population level, it is envisaged that Re-188 brachytherapy would sit permanently alongside other radiation therapy techniques in the management algorithm, as an alternative treatment technique appropriate only in limited specified clinical circumstances.

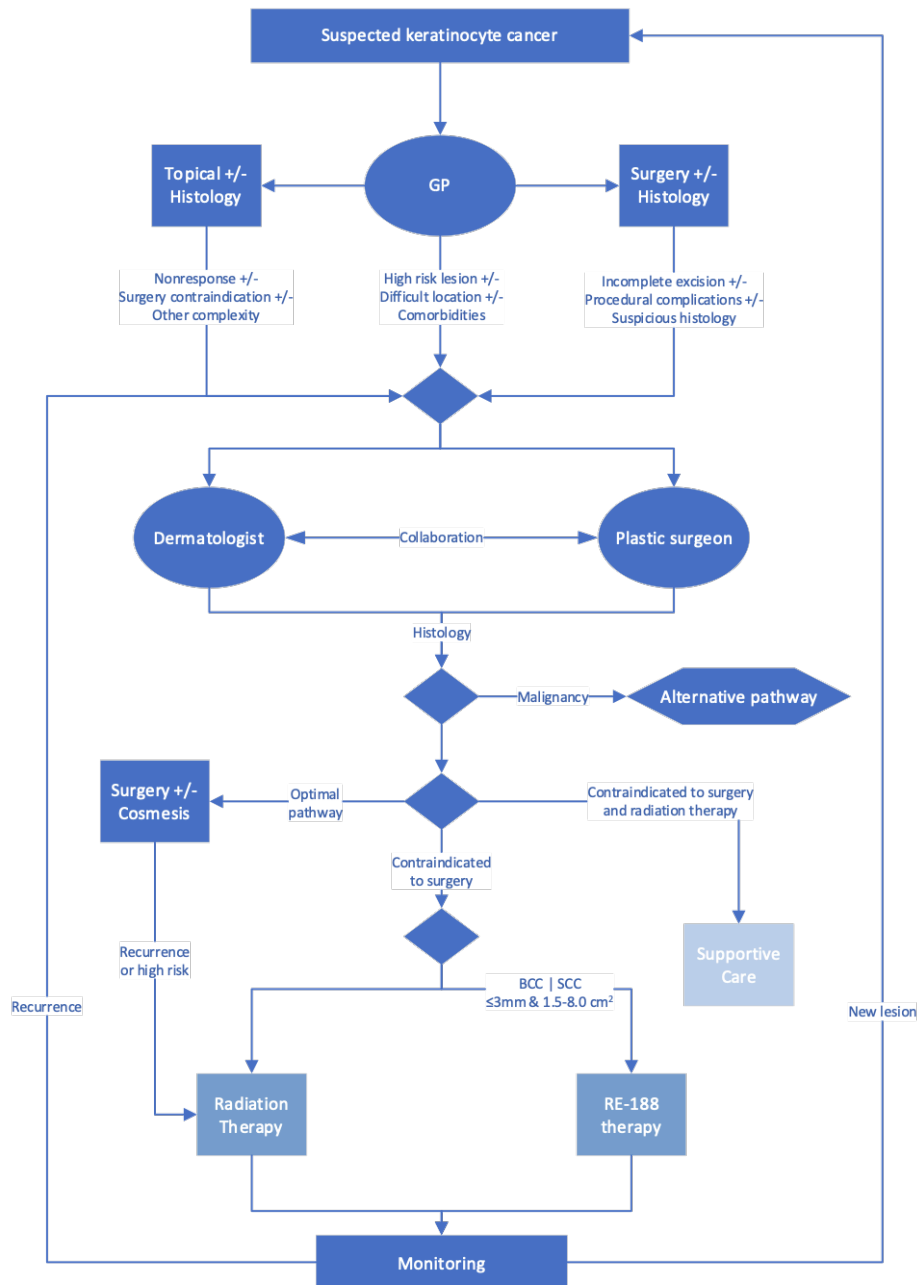


Figure 2 Proposed clinical management algorithm

Source: Figure 1-4, page 20 of MSAC 1657 ADAR+in-line commentary

Abbreviations: BCC= Basal Cell Carcinoma; GP= General Practitioner; SCC= Squamous Cell Carcinoma

8. Comparator

The comparator in the ratified PICO confirmation was radiation therapy which encompassed external beam radiation therapy (EBRT) and brachytherapy. Radiation therapy is an effective treatment that is well suited and currently used for primary treatment of the small proportion of patients with BCC and SCC that present particular problems for conventional surgery.

The ADAR defined radiation therapy as conventionally fractionated regimen of EBRT with either:

- 3D megavoltage EBRT (termed LINAC by the ADAR) – MBS items 15550, 15562, 15254 and 15700 or
- intensity modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT) – MBS items 5555, 15565, 15275 and 15715.

Note: LINAC (linear accelerator) can be used to deliver x-ray (photons) or electron beam RT, in 2D or 3D at low or high energies (megavoltage) and also IMRT/VMAT. Based on the MBS items selected by the ADAR, the ADAR reference to LINAC encompassed 3D megavoltage EBRT. Therefore, 3D megavoltage has been used throughout this document instead of LINAC.

While the clinical evidence base for EBRT included other EBRT modalities, such as superficial or orthovoltage x-ray EBRT, the ADAR did not include these EBRT modalities in the economic and financial analysis. Superficial and orthovoltage EBRT is commonly used for non-melanomatous skin cancer therefore exclusion of orthovoltage from EBRT comparator in the economic and financial analysis may not have been appropriate.

The ADAR also did not include brachytherapy as per the ratified PICO confirmation. The MBS includes a series of items for external brachytherapy for construction and application of a radioactive mould to an external surface and associated planning/verification services that can be used for treatment of keratinocyte cancers (15536, 15351, 15354, 15357 and 15800). The ADAR excluded brachytherapy based on the applicant's clinical expert advice that suggested the brachytherapy MBS items were rarely used for the treatment of keratinocyte cancers.

9. Summary of public consultation input

Consultation feedback was received from the following five organisations, including four (4) medical specialist colleges, one (1) consumer organisation and six (6) individual specialist physicians:

- Australasian Association of Nuclear Medicine Specialists (AANMS)
- Australasian College of Dermatologists (ACD)
- Australian Society of Plastic Surgeons (ASPS)
- Melanoma and Skin Cancer Advocacy Network (MSCAN)
- Royal Australian and New Zealand College of Radiologists (RANZCR).

MSCAN was broadly supportive of the application, while ACD, ASPS and RANZCR were broadly not supportive of the application. AANMS supported the application for the intended purpose but considered the application had been mis-titled with the inclusion of the word 'brachytherapy'. Further, AANMS also noted that the supporting evidence remains limited and is awaiting the results of the EPIC-Skin study.

The benefits of the proposed medical service for patients were considered to be:

- shorter treatment times meaning less time away from home, family, and work, particularly as the proposed intervention only requires one treatment
- it can be delivered without anaesthetic in an outpatient setting,
- the proposed intervention is a non-invasive pain-free alternative to surgery, particularly for thin lesions, or where surgery would be considered disfiguring, too difficult or not tolerated, especially on sensitive parts of the face, or BCC's in very hard to treat areas,
- it has a good cosmetic result,
- it appears to have a rapid turnaround from decision to treat to treatment.

MSCAN further stated that publicly funding the proposed intervention would increase access, while ensuring service delivery at a competitive and fair price and reduce public skin cancer waiting lists.

There were many disadvantages and concerns raised in the consultation feedback in regard to the proposed intervention such as:

- the application provided insufficient evidence of safety and efficacy for the proposed intervention including the durability of treatment, recurrence rates, long-term side effects/risks, and does not appear to provide a benefit over established radiation therapy technology,
- the studies in the application are mainly retrospective and very small, with the potential for conflict of interests for clinicians employed or paid by the technology-supplier, and the absence of randomised head-to-head comparison of the proposed treatment with the standard of care,
- the radiation safety and protection of patients and healthcare providers,
- risk of exceeding lifetime radiation limits in case of retreatments,
- adherence to procedures related to precise documentation of treated areas and administered radiation dose,
- most thin tumours are easily and effectively treated by other modalities especially surgery and the theoretical benefit of avoiding surgery due to concerns with general anaesthesia may not be realised as most surgeries for small thin lesions can be done under local anaesthesia,
- the treatment is incorrectly described as 'non-invasive', Rhenium-188 therapy is still radiotherapy with potential for long-term consequences,
- the proposed treatment could have technical disadvantages including in regard to the cost of the actual product and disposal of the nuclear waste,
- high dose-rate brachytherapy may cause an acute radiation skin reaction in the weeks following the treatment and that there is potential for significant long-term toxicity,
- the proposed intervention does not appear to provide improved radiation dose-distributions or dose-rates compared with current radiation oncology techniques such as standard dual modality LINACs, High Dose-Rate (HDR) afterloaders or Superficial X-Rays (SXR),
- the proposed setting is limited to accredited nuclear medicine facilities in public and private hospitals.

The feedback mostly supported the comparator nominated in the application, which was subsequently defined in the ratified PICO confirmation as radiation therapy, encompassing external beam radiation therapy and brachytherapy. However, RANZCR considered the main comparator would be superficial/orthovoltage radiation therapy as the application is for treatment of lesions less than 3mm thickness. RANZCR also noted that low energy electrons delivered using a LINAC would also be a viable alternative. Further, it is unlikely that VMAT would be a comparator except in difficult sites such as the scalp.

ACD considered that given the radiation protection considerations for provision of this treatment, the proposed setting of accredited nuclear medicine facilities in public and private hospitals is appropriate. RANZCR considered that the proposed treatment delivery in accredited nuclear medicine facilities in specialist hospitals could restrict patient access to treatment, especially as it would be difficult to offer the treatment regularly in regional, rural, and remote locations. This could result in treatment delays and negatively impact patients. MSCAN agreed with this, stating that they were interested to know whether treatment facilities would be limited to metropolitan areas, and that they advocate for equitable access for Australians living in rural and regional

Australia. AANMS noted that limiting treatment to comprehensive nuclear medicine facilities would provide the highest level of safety, however considered there could be restrictions in place initially which are reviewed after a comprehensive safety profile has been developed.

The individual specialists were particularly concerned with the proposal to target lesions in high-risk sites such as the lip. They considered that it would be impossible to gain informed consent as there is insufficient data to inform the patients about the efficacy and safety relative to other widely available treatment modalities.

AANMS considered that the referral pathway and proposed Medicare descriptors should allow access for GPs who specialise in skin cancer. Particularly as this may incur additional costs and limit access for the patients if referral to dermatologists and plastic surgeons is required. Current practice allows for direct referral from GP to radiation oncologists for assessment of appropriateness of treatment. AANMS also consider that the radiation specialist involved should be actively and directly involved in the application of the material.

10. Characteristics of the evidence base

No direct evidence comparing safety and effectiveness of Re-188 brachytherapy with EBRT in patients with BCC and SCC were identified.

Characteristics of the evidence for Re-188 brachytherapy

The ADAR included five single arm studies evaluating Re-188 brachytherapy in BCC and SCC. Key features of the relevant evidence base are summarised in Table 4. Risk of bias for the included studies was re-assessed in the commentary using Newcastle Ottawa Scale because the ADAR did not use an appropriate assessment tool. All five single arm studies had applicability issues. Studies included patients that had single or multiple lesions. In four studies that reported lesion size area, a proportion of patients (percentage not always estimable) had lesion surface area larger than the surface area specified in the ratified PICO confirmation (> 8.0 cm²). Studies also included patients where previous treatments had failed or they refused surgery in addition to patients who had contraindications to surgery. In one study³ which evaluated 15 patients, lesions of nine patients were classified as SCC *in situ* (Tis). These lesions are referred to as Bowen's disease and are out of scope for the ADAR. Very few outcomes were reported across the included studies.

Four of the included studies, on Re-188 brachytherapy, were conducted at a single hospital, S. Eugenio Hospital, Rome (Carrozzo et al. 2013, Sedda et al. 2008, Cipriani et al. 2017, Cipriani et al. 2020). The commentary noted that not enough information was available in the study articles to determine if the populations analysed in studies conducted at S. Eugenio Hospital in Rome are completely unique and independent of each other. There were some differences in the described populations and treatments within these studies, but also similarities in years the treatment was delivered (not reported for Sedda et al. 2008 and Cipriani et al. 2017) and follow-up duration.

Castellucci et al. 2021 was the best reported and the most applicable study for the ADAR.

³ Carrozzo A et al. (2013) "Dermo beta brachytherapy with 188-Re in squamous cell carcinoma of the penis: a new therapy." Eur J Dermatol 23 (2):183-8.

The ADAR noted that a manuscript for an unpublished study⁴ was available but did not incorporate it into the ADAR due to late availability of this data. The study was reviewed in the commentary, and it was determined that its addition to the evidence base would not affect the clinical conclusions as it was of similar quality, applicability and reporting to the evidence base presented in the ADAR.

The applicant's pre-ESC response provided interim statistical analysis an ongoing international trial phase IV open label single-arm study (the EPIC-Skin study⁵) with recruitment sites in Australia. The study (N=182) aims to evaluate the response to Re-188 brachytherapy in patients with non-melanoma skin cancer (80% of patients had BCC and 20% had SCC).

During the PICO confirmation stage, the applicant stated intentions to establish an international registry for keratinocyte cancers, which will include an Australian component to allow a better understanding of disease epidemiology as well the utility of Re-188 brachytherapy in its treatment. Patients from the EPIC-Skin study would also be included in the registry. No Australian registry data were available from the registry to inform the assessment of Re-188 brachytherapy. The pre-ESC response noted that work on the registry was initially delayed by work on the EPIC-Skin study but has now recommenced.

Table 4 Key features of the included evidence on Re-188 brachytherapy in patients with keratinocyte cancer

References	No. of patients	Design/duration	Risk of bias	Patient population	Surface area and thickness	No. of treatments	Outcome(s)
Castellucci 2021 ⁶	54	Single arm, prospective Follow-up: 33 months	Fair	BCC and/or SCC of the scalp, face, ears, fingers or another area where surgery or radiotherapy were difficult.	Surface area, mean (range) = 7.0 cm ² (1–36 cm ²), Thickness, mean (range) = 1.1 mm (0.2–2.5 mm)	1 treatment	Response to therapy Early skin toxicity Cosmetic results
Carrozzo 2013 ⁷	15	Single arm, prospective Follow-up: up to 5 years (mean= 51 months)	Fair	SCC of penis where previous treatments failed.	In situ (n =9) Verrucous (n=4) Micro-invasive (n= 2) Invasive (n= 1)	1-3 treatments	Response to therapy Pain/discomfort
Sedda 2008 ⁸	53	Single arm, prospective Follow-up: 20-72 months (mean= 51 months)	Fair	BCC and/or SCC of the head or neck (70%), upper and lower limbs (22%), trunk and back (8%) who either relapsed or	BCC surface area, mean (SD) = 7.04 (8.9) cm ² SCC surface area, mean (SD) = 14.6 (10.6) cm ²	1-3 treatments	Response to therapy

⁴ Tietze J et al. (2023) "Topical Rhenium-188 ionizing radiation therapy exerts high efficacy in curing invasive non-melanoma skin cancer." [Unpublished manuscript].

⁵ Rhenium-Skin Cancer Therapy (SCT) for the Treatment of Non-Melanoma Skin Cancer. (EPIC-Skin) – [NCTC 05135052](#)

⁶ Castellucci P et al. (2021) "High dose brachytherapy with non sealed (188)Re (rhenium) resin in patients with non-melanoma skin cancers (NMSCs): single center preliminary results." *Eur J Nucl Med Mol Imaging* 48 (5):1511-1521.

⁷ Carrozzo AM et al. (2013) "Dermo beta brachytherapy with 188-Re in squamous cell carcinoma of the penis: a new therapy." *Eur J Dermatol* 23 (2):183-8.

⁸ Sedda AF et al. (2008) "Dermatological high-dose-rate brachytherapy for the treatment of basal and squamous cell carcinoma." *Clin Exp Dermatol* 33 (6):745-9.

				surgery was not possible.			
Cipriani 2020 ⁹	52	Single arm, retrospective Follow-up had no regime (median= 296 days)	Poor	BCC, SCC, Bowen's disease or extramammary Paget's disease. Head and neck lesions (~73%)	Treated area, mean (range) = 9.79 (0.3 – 60.5) cm ² 57% of the areas were 2-10 cm ²	1 treatment	Response to therapy Complications
Cipriani 2017 ¹⁰	43	Single arm, retrospective mean= 288 days)	Poor	BCC, SCC all over body in whom surgery was not indicated or had previously failed.	Treated area, mean (range) = 5 (1-49) cm ²	1-2 treatments	Response to therapy

Source: Table 5, pg 14 of MSAC 1657 Commentary Executive Summary

Italic text represents the new information added by the commentary. The risk of bias was re-assessed by the Assessment Group using the Newcastle Ottawa Scale which is suitable for non-comparative cohort studies. The scoring system classifies studies as good, fair, or poor quality,

Abbreviations: BCC= basal cell carcinoma; SCC= squamous cell carcinoma

Characteristics of the evidence for EBRT

The ADAR identified 25 studies on EBRT in BCC and SCC as being sufficiently representative of the proposed population and comparator noting that the screening and selection process was based on imperfect reporting in the study publications, and subjective clinical judgement was used for determining eligibility. These include a small number of studies comparing EBRT with other treatment modalities (surgery or brachytherapy) and/or assessing different fractionation schedules/doses, while the rest employed a true single arm design. The ADAR commented that these studies span more than two decades and were of highly variable quality and applicability. The ADAR did not perform a formal quality assessment (risk of bias) of these studies but the single randomised controlled trial by Avril et al. 1997¹¹ was noted to be of highest quality but low applicability as it described a largely obsolete treatment modality used in the 1980s. Some of the more recent studies^{12,13,14} mainly evaluated hypofractionated regimens which the ADAR stated were not standard of care.

The ADAR claimed to compare the Re-188 brachytherapy to EBRT through an indirect comparison. However, the 25 studies on EBRT were only summarised narratively and not in a tabular format. The ADAR stated that tabulating the evidence was not possible due to the incompleteness and inconsistency of information in EBRT studies. As such the evidence was not

⁹ Cipriani C et al. (2020) "Personalized irradiation therapy for NMSC by rhenium-188 skin cancer therapy: a long-term retrospective study." *Journal of Dermatological Treatment*:1-7.

¹⁰ Cipriani C et al. (2017) "Personalized High-Dose-Rate Brachytherapy with Non-Sealed Rhenium-188 in Non-Melanoma Skin Cancer." *Int J Nuc Med Res Jul*:114-22.

¹¹ Avril MF et al. (1997) "Basal cell carcinoma of the face: surgery or radiotherapy? Results of a randomized study." *Br J Cancer* 76 (1):100-6.

¹² Ferini G et al. (2021) "A small case series about safety and effectiveness of a hypofractionated electron beam radiotherapy schedule in five fractions for facial non melanoma skin cancer among frail and elderly patients." *Rep Prac Onc and Rad* 26 (1):66-72.

¹³ Ferro MF et al. (2015) "Short-course radiotherapy in elderly patients with early stage non-melanoma skin cancer: a phase II study." *Cancer Invest* 33 (2):34-8.

¹⁴ Haehl E et al. (2021) "The value of primary and adjuvant radiotherapy for cutaneous squamous cell carcinomas of the head-and-neck region in the elderly." *Radiat Oncol* 16 (105):1-13.

presented in a format that would allow an indirect comparison between Re-188 brachytherapy and EBRT.

The studies on EBRT were reviewed for inclusion in the commentary. The main issue when trying to establish comparability of the populations between Re-188 brachytherapy and EBRT studies was that EBRT studies did not provide details of lesion area or depth but used TNM¹⁵ staging system instead. When reassessing the inclusion of EBRT studies in the commentary, only studies with at least ~ 80% of lesions classified as T1 (< 2 cm) or T2 (2 to 5 cm) were included due to lack of information on lesions size and depth. These criteria were met by 17 out of 25 studies. The commentary prepared tabular summaries to synthesise the ADAR's narrative review of EBRT for following outcomes: treatment response, toxicity, and cosmetic results to assist MSAC. However, the issue remains that there is no direct nor indirect comparison of Re-188 brachytherapy versus EBRT. The commentary considered the ADAR clinical evidence presentation was insufficient to evaluate the comparative safety and effectiveness of Re-188 brachytherapy and EBRT for BCC and SCC.

11. Comparative safety

Safety data for Re-188 brachytherapy and EBRT in BCC and SCC are summarised in Table 5 and Table 6, respectively.

For studies evaluating Re-188 brachytherapy, one study (Catellucci et al. 2021) with 50 patients reported acute skin toxicity using Common Terminology Criteria for Adverse Events (CTCAE 5.0). Four events were classified as Grade 3 while the remaining 56 events were either Grade 1 or Grade 2. The remaining four studies simply noted general observations relating to pain during application, discomfort, and contamination. No other safety outcomes were reported in the included studies. For EBRT studies, adverse events were reported as a proportion of the treated population or as a proportion of treated lesions. Grade 3 events or higher were rare and only observed in 2 out of 5 studies.

The commentary noted that the ADAR did not address the safety of retreatment and treatment of adjacent tumours as specified in the ratified PICO confirmation (MSAC 1657 Ratified PICO Confirmation, pg 10). The applicant's pre-ESC response did not address treatment of multiple lesions. Regarding retreatment, the pre-ESC clarified that while early trials allowed multiple treatment episodes per lesion, the more recent data relates to a single episode of treatment. As such the applicant neither proposed nor anticipated that more than one instance of Re-188 brachytherapy per lesion will be required and that in rare cases of non-response, initiation of an alternative treatment approach is a more likely outcome.

The applicant's pre-ESC response also provided interim statistical analysis from the ongoing EPIC-Skin study. The interim analysis indicated the majority of patients had no pain or discomfort at 14 days. However, 24 patients experienced adverse events (such as pain, swelling and wound infection), and one patient had a serious adverse event relating to wound healing.

¹⁵ In the TNM staging system, T refers to the size and extent of the main tumour, N refers to the number of tumour-involved lymph nodes and M refers to whether the tumour has metastasised.

Table 5 Results of safety across the included studies for Re-188 brachytherapy

Study ID	No. of patients	Number of treatments	Risk of bias	Safety outcome, follow-up	Results reported
Castellucci 2021	54	1 treatment	Fair	Acute skin toxicity (CTCAE) 30 days	Grade 1: 31 events (51.6%) Grade 2: 25 events (41.6%) Grade 3: 4 events (6.6%)
Carrozzo 2013	15	1-3 treatments per patient (single treatment per lesion)	Fair	No formal safety assessment	0 patients reported discomfort. 0 patients had collateral effect from therapy.
Sedda 2008	53	1-3 treatments (single, n= 43; two, n= 8; three, n= 2)	Fair	No formal safety assessment	Mild erythema immediately after treatment (cleared 2-7 days after). Bleeding often present for large lesions (cleared 10-30 days after treatment). 0 patients reported disfiguring scarring, pain or side-effects. 0 patients reported systemic or topical side effects (20-72 months after treatment).
Cipriani 2017	52	1-2 treatments	Poor	No formal safety assessment	No side-effects or adverse events reported during treatment. No contamination found.
Cipriani 2020	43	1 treatment	Poor	No formal safety assessment	No complications were reported post treatment. No contamination found.

Source: Table 6, pg 17 of MSAC 1657 Commentary Executive Summary
Abbreviations: CTCAE= Common Terminology Criteria for Adverse Events

Table 6 Results of safety across the included studies for EBRT

Study ID	Fractionation / dose	Safety measure	Grade 1	Grade 2	Grade 3	Grade 4	
Ferini 2021	35 Gy per 5 fractions; 6 MeV electron beam	Acute skin toxicity (CTCAE) 4 week follow-up	12/23 (52.2%)	8/23 (34.8%)	3/23 (13.0%)	0%	
Ferro 2014	30 Gy per 6 fractions; Electrons (6-9-12 MeV) or megavoltage photons (6 MV)	Acute toxicity (CTCAE)					
		Skin hyperpigmentation	4/31 (12.9%)	0%	0%	0%	
		Itch	1/31 (3.2%)	0%	0%	0%	
		Skin pain	1/31 (3.2%)	0%	0%	0%	
		Dry skin	10/31 (32.3%)	0%	0%	0%	
		Others	3/31 (9.7%)	0%	0%	0%	
		Late toxicity (EORTC-RTOG)					
		Cutaneous hyperpigmentation	4/31 (12.9%)	0%	0%	0%	
		Skin atrophy	11/31 (35.5%)	0%	0%	0%	
Fibrosis	1/31 (3.2%)	0%	0%	0%			
Olschewski 2006	5 X 3 Gy per week, total of 57 Gy (95% of patients); Low energy photons 950 to 100 kV)	Acute toxicity CTC Score (6 weeks after RT)	46%	0%	0%	0%	
		Late toxicity					
		Pigmentation changes	43/104 (41%)	53/104 (51%)	0%	0%	
		Telangiectases	0%	0%	0%	0%	
		Fibrosis	45/104 (43%)	0%	0%	0%	
Pampena 2016	Two different schedules: Group A (7 weekly fractions of 525 cGy), Group B (15 daily fractions of 300 cGy)	Acute toxicity	Weekly 0	Weekly 7/236	Weekly 1/236	Weekly 6/236	
			Daily 0	Daily 2/149	Daily 2/236	Daily 2/236	
Russi 2015	Orthovoltage or electron beams, 25 or 30 Gy in 5 or 6 fractions of 5 Gy, once weekly in 5 or 6 weeks	Acute skin toxicity (CTCAE)	Grade 1/Grade 2 41/134 (30.6%)		0%	0%	

Source: Commentary Table 4, pg 57 of MSC 1657 ADAR+in-line commentary

Abbreviations: CTC= Common Toxicity Criteria; CTCAE = Common Toxicity Criteria for Adverse Events; EORTC-RTOG = European Organization for Research and Treatment of Cancer Radiation Therapy Oncology Group

12. Comparative effectiveness

Effectiveness data for Re-188 brachytherapy in BCC and SCC are summarised in Table 7.

Complete and partial response data for EBRT studies are summarised in Table 8 and cosmetic results are summarised in Table 9.

For Re-188 brachytherapy, five single arm studies reported the treatment response rate to Re-188 brachytherapy at varying follow-up timepoints. Only one study (Catellucci et al. 2021) provided a definition of complete and partial response. The other four studies lacked this information. In three studies (Sedda et al. 2008, Cipriani et al. 2017, Cipriani et al. 2020) complete response was assessed as 100% (of patients) during a 3 to 5 month follow-up. One small study (Carrozzo et al. 2013) with 15 participants found that in patients with SCC of penis, complete response was 80% (12 out of 15) after 3 to 5 months follow-up. Castellucci et al. 2021 reported complete response rates of 98.2% (53 out of 54), 100% (41 out of 41) and 96% (23 out of 24) for evaluable lesions which had histology and dermoscopy results available at 6, 12 and 24 months.

Cosmetic results were reported by Castellucci et al. 2021 and were evaluated in 41 evaluable lesions according to Radiation Therapy Oncology Group (RTOG) criteria. Cosmesis was graded good in 11 out of 41 lesions and graded excellent for 30 out of 41 lesions.

No other effectiveness outcomes were reported in the studies for Re-188 brachytherapy.

The applicant's pre-ESC response provided interim statistical analysis from the ongoing EPIC-Skin study. The interim analysis indicated complete response in 97.2% of patients at 6 months

For EBRT studies, complete response was observed in more than 94% of patients in each study (range: 94.1% to 100%) at various timepoints. Definitions for the cosmetic scoring options for each EBRT study varied based on the scale, treatment modality and site of the lesions. In the majority of studies cosmetic outcomes were more likely to be classified as Excellent and/or Good than Fair/Acceptable or Poor/Not acceptable.

Table 7 Results of effectiveness across the included studies for Re-188 brachytherapy

Study ID	No. of patients	Risk of bias	3-5 months	6 months	12 months	24 months	≈48 months
Response to therapy							
Castellucci 2021*	54	Fair	NA	CR:53/54 (98.2%) PR:1/54 (1.8%) NR: 0/54 (0%)	CR:41/41 (100%) PR: 0/41 (0%) Relapse: 0%	CR: 23/24 (96%) PR: 0/24 (0%) Relapse:1/24 (4%)	NA
Carrozzo 2013	15	Fair	CR:12/15 (80%) NR: 2/15 (13%) LTFU:1/15 (0.6%)	NA	NA	NA	NA
Sedda 2008	53	Fair	CR: 100%	NA	NA	NA	CR: 100%
Cipriani 2017	52	Poor	CR: 100%	NA	NA	NA	NA
Cipriani 2020	43	Poor	CR: 100%	NA	NA	NA	NA
Cosmesis							
Castellucci 2021	50	Fair	NA	NA	Good: 11 (26.8%) Excellent: 30 (73.1%)	NA	NA

Source: Table 8, pg 19 of MSAC 1657 Commentary Executive Summary

*Results were reported per lesion: Complete responders if the dermoscopy did not show any suspected area of persistence of the disease that may deserve a biopsy or if the biopsy result guided by the dermoscopy was negative; Partial responders if the biopsy result on a suspected area was positive but the treatment with Rhenium-SCT® caused a significant reduction in the extent of the lesion making possible the surgical excision or other local therapies with subsequent complete histological response

CR= complete response; PR= partial response; NR= no response; LTFU= lost to follow up; NA= not applicable; RTOG= Radiation Therapy Oncology Group

Table 8 Results of treatment response (complete response) outcomes across the EBRT studies

Study ID	Follow-up	n/N (%)
Complete response		
Ferini (2021)	6 months	22/23 (95.7%)
Ferro 2014	3 months	30/31 (96.8 % . 95% CI: 83.3-99.9%)
Olschewski 2006	24 months	100%
Piccinno 2020	1 month	100%
Russi 2015	NR	157/159 (98.7%) BCCs 132/134 (98.5%) patients
Caccialanza 2014	29 months (median)	122/127 (96.06%)
Caccialanza 2009	1 month	663/ 671 (98.8%)
Caccialanza 2005	1 month	111/115 (96.52%)
Caccialanza 2003	1 month	381/405 (94.1%)
Partial response		
Ferini (2021)	6 months	1/23 (43 %) (T4 lesion)
Ferro 2014	3 months	1/31 (3.2 %)
Caccialanza 2014	29 months (median)	1/127 (0.78%)
Caccialanza 2009	1 month	3/671 (0.44%)
Caccialanza 2005	1 month	1/115 (0.87%)

Source: Commentary Table 5, pg 61 of MSAC 1657 ADAR+in-line commentary
Abbreviations: BCC= basal cell carcinoma; NR= not reported

Table 9 Results of cosmetic outcomes across the EBRT studies

Study ID	Timepoint	Excellent	Good	Fair/ Acceptable	Poor/ Not acceptable
Ferro 2014	27 months	12/27 (44.4%)	14/27 (51.9%)	1/27 (3.7%)	NA
Olschewski 2006	24 months	39/104 (38%)	58/104 (56%)	7/104 (6%)	NA
Pampena 2016	32 months (median)	Weekly group: 212/275 (77%) Daily group: 143/161 (88.8%)	Weekly group: 22/275 (8%) Daily group: 10/161 (6.2%)	Weekly group: 6/275 (2.2%) Daily group: 0/161 (0%)	Weekly group: 4/275 (1.4%) Daily group: 2/161 (1.3%)
Avril 1997/Petit 2000	48 months	NA	75/113 (69%)	24/112 (22%)	9/112 (8%)
Piccinno 2020	39 months (median)	NA	8/47 (17%)	39/47 (83%)	0%
Caccialanza 2014	NR	NA	77/122 (62.3%)	34/122 (27.1%)	4/122 (4.1%)
Van Hezewijk 2010*	54 Gy group: 66 months 44 Gy group: 22 months	NA	54 Gy group: 38% 44 Gy group: 33%	54 Gy group: 49% 44 Gy group: 50%	54 Gy group: 13% 44 Gy group: 17%
Caccialanza 2009	NR	NA	496/671 (74.5%)	149/671 (22.4%)	16/671 (2.4%)
Caccialanza 2003	NR	NA	289/381 (75.9%)	82/381 (21.5%)	9/381 (2.4%)

Source: Commentary Table 6, pg 62 of MSAC 1657 ADAR+in-line commentary

* Also reported patient assessed cosmetic outcomes. Cosmetic scoring options for each study: Excellent, Good, Fair (Ferro 2014), Excellent, Good, Fair, Poor (Olschewski 2006; Pampena 2016), Good, Fair, Poor (Avril 1997/Petit 2000, Van Hezewijk 2010), Good, Acceptable, Not acceptable (Piccinno 2020, Caccialanza 2009, Caccialanza 2003)

Abbreviations: NA= not applicable; NR= not reported;

Clinical claim

The ADAR stated that the evidence available to inform a comparative clinical evaluation of Re-188 brachytherapy and EBRT within the proposed MBS setting had significant limitations which prevent the ADAR from making any formal clinical claims. Specifically, that the evidence presented consisted of ‘two discrete sets of heterogenous, essentially single-arm, prospective and retrospective, investigator-initiated studies, conducted in a wide range of patient populations and clinical settings, over 50 years’. Despite this statement, the ADAR concluded that Re-188 brachytherapy is likely to provide generally similar effectiveness and safety to a conventionally fractionated regimen of EBRT using either 3D megavoltage or IMRT/VMAT technologies. However, due to the paucity and limitations of the available evidence, the commentary considered that a clinical claim of uncertain comparative safety and effectiveness is probably more appropriate.

MSAC considered that the comparative effectiveness and safety Re-188 brachytherapy versus EBRT was uncertain at this time. MSAC noted the final peer-reviewed results from the international EPIC-Skin study may assist with MSAC decision-making regarding the ADAR’s clinical claims.

13. Economic evaluation

The ADAR presented a cost comparison analysis that compared the MBS funded healthcare resources for EBRT against Re-188 brachytherapy instead of a cost-effectiveness or cost-utility analysis as proposed in the ratified PICO confirmation. The ADAR justified this approach based on the clinical claim being downgraded to non-inferior safety and effectiveness and due to limited availability of data. The commentary noted that the cost-comparison approach may be appropriate due to the limited clinical evidence, differences in cost structures between the intervention and comparator and an absence of existing economic evaluations with Re-188 brachytherapy as an intervention for patients with non-melanoma skin cancer found in the literature review.

A summary of the economic evaluation is detailed in Table 10.

Table 10 - Summary of the economic evaluation

Component	Description
Perspective	Medicare Benefits Schedule (MBS) perspective
Population	Patients with confirmed Basal Cell Carcinoma (BCC) or Squamous Cell Carcinoma (SCC) <ul style="list-style-type: none"> • Maximum depth 3.0 mm; and • Area between 1.5-8.0 cm²; and • On the nose, eyebrow, lip, ear, digit, genitalia, shin or collarbone or a contiguous area; and • With comorbidities preventing surgery; or who have refused surgery
Prior testing	N/A
Comparator	External beam radiation therapy (EBRT) <ul style="list-style-type: none"> • Using a conventional fractionation regimen and delivered by: • 3D megavoltage (referred to as LINAC -Linear accelerator in the ADAR); or • Intensity modulated radiation therapy (IMRT); or • Volumetric modulated arc therapy (VMAT)
Type(s) of analysis	Cost-comparison analysis
Outcomes	Total treatment cost
Time horizon	Discrete time horizon
Computational method	Discrete event simulation
Generation of the base case	Modelled
Software	Excel

Source: Table 11, pg 23 of MSAC 1657 Commentary Executive Summary

Inputs and assumptions

The commentary noted that an MBS perspective was used for the economic evaluation, where the costs for EBRT may be well defined. However, whilst these MBS costs may be sufficient to estimate the total treatment costs for EBRT, there is limited available clinical and economic evidence to support the costing of Re-188 brachytherapy. Therefore, further clarification is required by the Applicant’s clinical experts to justify these cost components to aid ESC and MSAC decision-making.

The commentary also noted that the lack of long-term data to inform the economic evaluation limits the ability to determine other potential adverse events of both technologies and therefore can reduce the accuracy of the economic evaluation.

The ADAR used a random simulation of 100 lesion sizes (between 1.5 to 8 cm) and EBRT fractionations (between 10 to 30 fractionations) across a uniform distribution to determine the average total treatment cost of Re-188 brachytherapy and EBRT. The Commentary noted that the uniform distribution assumes all patients are equally likely to have a non-melanoma skin lesion of any size (within the specified range). This is unlikely to occur in clinical practice, as detailed by the patient populations in the clinical evaluation studies for Re-188 brachytherapy, where a normal or right-skewed patient distribution is present. The Commentary highlighted that a simulation of only 100 lesions may not provide enough patient cases to ensure the model is robust. However, as the economic analysis uses uniform distribution sampling, increasing the amount of cases will not influence the average treatment cost as a uniform distribution doesn't abide by the central limit theorem.

The commentary also noted that the relationship between lesion size and fractionation range is unclear and this becomes an issue in the comparison of average treatment costs between Re-188 brachytherapy and EBRT. The commentary considered more evidence of the relationship between the two technologies is required to ensure an accurate comparison of the average treatment costs between EBRT and Re-188 brachytherapy. The commentary noted that the gray (Gy) range may be an appropriate alternative method to establish a relationship between lesion size and fractionations, however this needs further clinical input.

Re-188 brachytherapy

The cost of an individual procedure is defined by the proposed (fully inclusive) 100% MBS Schedule Fee for the three "tiered" items proposed. An overall average treatment cost has been calculated based on a random sample of 100 lesions with a reasonably conservative uniform size distribution of between 1.5 and 8.0 cm².

As discussed in section 4, the commentary noted that the type of cost components for Re-188 brachytherapy included in the all-inclusive proposed MBS fee for Re-188 brachytherapy may be appropriately defined given the clinical workflow depicted in Figure 1. However, further clarification is required from the Applicant's clinical experts to justify the estimated cost for each of the components to aid ESC and MSAC decision-making.

The commentary noted that the cost of one carpoule of Re-188 is \$14,000 and can treat up to 18cm², which is approximately 2 to 4 patients with 1 lesion sized 5-8 cm² or 6 to 12 patients with 1 lesion sized 1.5-3 cm². The ADAR estimated the cost per patient for one lesion treatment with Re-188 brachytherapy but did not include any wastage costs for the Re-188 compound. The amount of wastage and the associated costs will vary depending on how efficiently lesions are batched (potentially \$777 per cm² wastage). ESC noted that it was not clear whether one carpoule can treat up to 18 cm² (as stated in the ADAR) or up to 25 cm² (as stated in the ratified PICO confirmation). ESC noted that if one carpoule can treat an area of 25 cm², the cost across the 3 proposed items reduces from \$3,420 - \$6,720 (if assume 18 cm²) to \$2,930 - \$5,338 (if assume 25 cm²).

The pre-MSAC response did not confirm and justify the appropriate area (18 cm² or 25 cm²) to inform the costings but acknowledged the issues raised by ESC and stated a willingness to with MSAC and the department to better estimate the costs of providing the service (which will likely vary significantly between clinics), establish the most appropriate tier structure for the item fees and ultimately arrive at an MBS listing which will encourage efficiently delivery of the service (with appropriate batching of patients) and minimise inequitable and undesirable out of pocket costs for patients.

According to the clinical evaluation section in the ADAR, the included studies had a proportion of patients who had lesion sizes that were larger than 8 cm² (Table 4). The commentary

recommends that while a lesion range of 1.5 to 8 cm² was used in the analysis which is consistent with the population description in the ratified PICO confirmation (MSAC 1657 Ratified PICO Confirmation, pg. 2), further justification of how this range was defined may be useful.

The commentary noted that the economic evaluation did not consider more than one Re-188 brachytherapy treatment per patient. The ratified PICO confirmation indicated that “around 85% of patients require only a single treatment” (MSAC 1657 Ratified PICO Confirmation, pg. 20). Additionally, three out of the five Re-188 brachytherapy studies stated that the Re-188 brachytherapy treatment consisted of one to two, or three treatments. Therefore, the commentary conducted a scenario analysis where 85% of patients have one Re-188 brachytherapy treatment and the remaining 15% have two treatments (Table 14).

EBRT

As noted in Section 6 – Comparator, the ADAR assumed that the EBRT modalities used would be either 3D megavoltage electron EBRT (referred to as LINAC) or IMRT/VMAT. That is, the treatment costs for EBRT were based on MBS items for 3D megavoltage EBRT (LINAC) and MBS items for IMRT/VMAT. The ADAR assumed all patients receiving EBRT will have one initial specialist consultation with a dermatologist or plastic surgeon (MBS Item 104) for diagnosis and referral and three follow up consultations with the same specialist (MBS Item 105) during and at the completion of their course of treatment, irrespective of the specific fractionation regimen or technical modality employed. The ADAR also assumed patients require three episodes of wound dressing (MBS Item 30003: 100% Schedule Fee: \$38.40) during their treatment course. The commentary noted that the services provided for LINAC and IMRT/VMAT may be appropriate given the protocol for skin cancer BCC definitive EBRT.¹⁶

The ADAR assumed that patients required a single instance of both simulation and dosimetry per treatment course, and between 10 and 30 episodes of treatment and verification, depending on the prescribed fractionation regimen. The ADAR stated that the range of fractionation regimens considered was informed by local and international treatment guidelines and targeted consultation with local clinicians. The averaged number of fractionations applied was 19.03 based on the simulation of a random sample of 100 lesions, with a uniform distribution of between 10 and 30 dose fractions.

The ADAR also assumed that the EBRT modality used would be evenly split between 3D megavoltage (50%) and IMRT/VMAT (50%). The ADAR suggested that based on the total MBS utilisation patterns between 3D megavoltage and IMRT/VMAT items and targeted consultation with local clinicians, 50:50 weighting was a relatively conservative assumption, with the true proportion of relevant services provided using IMRT/VMAT technologies being significantly higher.

The following issues with the costing of the EBRT comparator were noted by the commentary and ESC:

- Other EBRT modalities

Orthovoltage is an alternative EBRT modality commonly used for treatment of BCC and SCC and would be a more suitable comparator for technologies that target superficial tumours. However, orthovoltage was not included as an EBRT modality in the ADAR. Therefore, sensitivity analyses including orthovoltage in the EBRT comparator have been included (see Table 14).

¹⁶ eviQ, Skin cancer basal cell carcinoma definitive EBRT, Accessed at: <https://www.eviq.org.au/radiation-oncology/skin/1032-skin-cancer-basal-cell-carcinoma-definitive-e#dose-prescription>.

- 3D megavoltage EBRT referred to as 'LINAC'

The ADAR included 'LINAC' as an EBRT modality. Although LINAC can be used to deliver x-ray or electron beam RT, in 2D or 3D, at low or high energies (megavoltage) and also IMRT/VMAT, the ADAR costed 'LINAC' using MBS items for 3D megavoltage EBRT (including simulation, dosimetry, treatment and verification). ESC advice is that 2D rather than 3D electron beam EBRT would be used for treatment of shallow and small ($\leq 3\text{mm}$) BCC or SCC (see Table 14 for ESC requested sensitivity analyses).

- Number of fractions

The ADAR assumed a fractionation range of 10-30 fractions would be used, with an average of 19.03 fractions from the 100 sample simulation. The commentary noted that the Gy range of 23 to 47gy was used in one of the Re-188 brachytherapy studies¹⁷ and according to EviQ guidelines, for a prescription dose of up to 50 Gy, the fractionation range is 5 to 20, as opposed to the 10 to 30 range used in the ADAR.¹⁸ Additionally, the commentary noted that the standard curative dose schedules for the treatment of small lesions (< 2 cm) typically require fewer treatments (4 to 12 treatments over 1 to 2 weeks) compared with larger lesions which require 15 to 30 treatments over 3 to 6 weeks.¹⁹ Furthermore, according to Khong et al,²⁰ treatment for low-risk BCC and SCC (early-stage tumours) involves 5 to 15 fractions daily (administered Monday to Friday). The commentary included additional scenario analysis to test the impact of different fractionation ranges in the economic evaluation (Table 14Table 14). In addition, ESC advice was that generally 5-10 fractions would be most common.

Table 11 below compares how the EBRT comparator was costed in the ADAR and revised by the commentary and ESC.

¹⁷ Paolo et al. (2020) "High dose brachytherapy with non sealed 188Re (rhenium) resin in patients with non-melanoma skin cancers (NMSCs): single center preliminary results"

¹⁸ eviQ, Radiation Oncology, Skin cancer basal cell carcinoma definitive EBRT, Accessed at: <https://www.eviq.org.au/radiation-oncology/skin/1032-skin-cancer-basal-cell-carcinoma-definitive-e>.

¹⁹ Cancer Council Australia, 8. Radiotherapy, Clinical practice guidelines for keratinocyte cancer, Accessed at: https://wiki.cancer.org.au/australia/Guidelines:Keratinocyte_carcinoma/Radiotherapy#cite_note-Citation:Grossi_Marconi_D.2C_da_Costa_Resende_B.2C_Rauber_E.2C_de_Cassia_Soares_P.2C_Fernandes_JM_Junior.2C_Mehta_N.2C_et_al_2016-11.

²⁰ Australian Journal of General Practice (AJGP), Jeremy Khong, Non-melanoma skin cancer in general practice: Radiotherapy is an effective treatment option, Volume 49, Issue 8, August 2020

Table 11 – Summary of EBRT costing in the ADAR and revised by the commentary and ESC

Input	ADAR	Commentary ¹	ESC ²
3D megavoltage	\$4,351.25	\$4,351.25	-
2D electron beam	-	-	\$1,315.93
IMRT/VMAT	\$9,821.73	\$9,821.73	\$7,343.90
Orthovoltage	-	\$1,098.01	\$642.45
Average # of fractions ³	19.03	19.03	10
EBRT weighting			
Electron beam	50% (3D)	5% (3D)	70% (2D)
IMRT/VMAT	50%	5%	10%
Orthovoltage	-	90%	20%
Weighted EBRT cost	\$7,086.49	\$1,696.86	\$1,748.03

Source: Constructed by the Department from information on pg 14 and Commentary Table 9 of MSAC 1657 ADAR+in-line commentary and ESC advice.

Abbreviations: ADAR = Applicant Developed Assessment Report; EBRT = external beam radiation therapy; ESC = Evaluation Sub-Committee; IMRT = Intensity-Modulated Radiation Therapy; VMAT = Volumetric modulated arc therapy

Notes:

1. In the commentary, the EBRT comparator costings were amended to include orthovoltage as a comparator: initial consult (MBS 104), follow up visit (MBS 105), treatment (MBS 15100). No simulation, dosimetry or verification MBS items required.
2. Costings of the EBRT comparator were amended to include orthovoltage (see note 1), revise the costs for electron beam from 3D to 2D electron beam: same initial follow up and wound care MBS items; simulation (MBS 15500), dosimetry (MBS 15527) and treatment (MBS 15254); no verification MBS item required; and amend the number of fractions from 19.03 to 10.
3. Applied to all EBRT modalities

Results of the base-case economic evaluation

The ADAR claimed that the cost of Re-188 brachytherapy will vary predictably (but non-linearly) by lesion size, while the cost of the EBRT comparator is less predictably variable by both technological approach (3D megavoltage vs. IMRT/VMAT) and the number of fractions used. This is based on a variety of factors including lesion size and anatomical location, patient/lesion characteristics, availability of the respective technologies, and individual clinician/patient preferences. The results in the ADAR have therefore been presented as a range of estimated treatment costs for the respective technologies, across their relevant dependent variable, and then as an expected “average” treatment cost, given independent (uniform) distributions of lesion sizes and dose fractionation regimens, and a specified mix of comparator technologies.

Over a simulated population of 100 lesions uniformly distributed between 1.5 and 8.0 cm², the average total treatment cost for Re-188 brachytherapy was estimated to be \$5,438. Across an independently simulated population of 100 lesions treated with 10 to 30 (uniformly distributed) EBRT fractions, the average total treatment cost for 3D megavoltage was estimated to be \$4,351 and that for IMRT/VMAT to be \$9,821. Assuming a weighted average of 50% 3D megavoltage and 50% IMRT/VMAT, the overall average cost of EBRT was estimated to be \$7,086.

Based on the estimated difference in treatment costs between the proposed intervention and main comparator, the ADAR estimated an average saving of \$1,648 per patient (Table 12).

The commentary noted that due to the high level of uncertainty regarding the relationship between lesion size and fractionations for Re-188 brachytherapy and EBRT, the results of the economic model may not be robust. More evidence of the relationship between the two technologies is required to ensure an accurate comparison of the total cost between two technologies.

Table 12 Results of the economic evaluation for Re-188 vs EBRT (3D megavoltage & IMRT/VMAT)

Parameter	Re-188 brachytherapy	EBRT (3D megavoltage & IMRT/VMAT)	Difference
Average treatment costs	\$5,438	\$7,086	- \$1,648
Cost saving			\$1,648

Source: Table 12, pg 26 of MSAC 1657 Commentary Executive Summary

Abbreviations: EBRT = External Beam Radiation Therapy; IMRT = Intensity-Modulated Radiation Therapy; Re-188 = Rhenium 188; VMAT = Volumetric modulated arc therapy

ADAR sensitivity analyses

The ADAR conducted a limited range of one-way sensitivity analyses (Table 13). All outcomes from the sensitivity analysis demonstrated Re-188 brachytherapy cost saving compared to EBRT (3D megavoltage & IMRT/VMAT). The analyses varied the:

- comparator mix (3D megavoltage:IMRT/VMAT) from 50:50 to 75:25 or 25:75
- respective distribution of cases from uniform (1.5-8.0 cm² | 10-30 fractions) to left or right skewed PERT distributions within the same intervals; and
- proposed MBS item fees for Re-188 brachytherapy by +/- 25%.

The Commentary noted that whilst the ADAR included an arbitrary sensitivity analysis that tested the upper and lower bounds of the MBS item fee for Re-188 brachytherapy, it is unclear what uncertainty this sensitivity analysis is attempting to address.

The commentary noted that a PERT distribution creates a curve that fits well to normal or lognormal distributions. However, to ensure the simulation is robust more clinical input is required as there remains a degree of uncertainty with this distribution. The results of the sensitivity analysis demonstrate that with a PERT distribution, Re-188 brachytherapy remains less costly when compared to EBRT.

Table 13 Sensitivity analyses

Sensitivity analysis	Base Case	Worst case		Best case	
	Value	Value	Result	Value	Result
Base case difference: -\$1,648.08					
Comparator mix (3D megavoltage:IMRT/VMAT)	50:50	75:25	-\$280.46	25:75	-\$3,015.70
Case distribution (Re-188 brachytherapy)	Uniform	Right skewed (6.5)	-\$638.76	Left skewed (2.25)	-\$2,867.44
Case distribution (EBRT)	Uniform	Left skewed (15)	-\$1,175.17	Right skewed (25)	-\$2,476.16
MBS item fees (Re-188 brachytherapy)	\$3,420-6,726	\$4,275 to \$8,407	-\$322.97	\$2,565 to \$5,044	-\$2,973.20

Source: Table 3-2, pg146 of MSAC 1657 ADAR+in-line commentary

Abbreviations: EBRT = External Beam Radiation Therapy; IMRT = Intensity-Modulated Radiation Therapy; MBS = Medicare Benefits Scheme; Re-188 = Rhenium 188; VMAT = Volumetric Modulated Arc Therapy

Additional sensitivity analyses on ADAR base case

Additional sensitivity analyses, undertaken by the commentary and the department at the request of ESC, are presented in Table 14. These sensitivity analyses explore the impact of:

- multiple Re-188 treatments
- inclusion of orthovoltage as one of the EBRT modalities
- amendment of the ADAR 3D megavoltage costs to 2D electron beam costs

- adjustment of the EBRT fractionation number.

The results of the sensitivity analyses indicate Re-188 is more costly than EBRT when orthovoltage is included, when the electron beam costs are changed from 3D to 2D and when the number of fractions is reduced.

The applicant's pre-MSAC response refuted the inclusion of orthovoltage stating the EBRT modalities used in the economic analysis was based on the advice of clinical expert's experienced in treating the of complex keratinocyte cancers. As such the applicant did not accept that orthovoltage represents a contemporary standard of care commonly used for treatment of BCC or SCC in contemporary Australian clinical practice and did not accept the validity that of the sensitivity analysis presented by the commentary where the EBRT modality split was changed to include 90% orthovoltage. Similarly, the fractionation ranged used in the ADAR was informed by targeted local clinical consultation. However, the applicant accepted that there is some uncertainty regarding the appropriate weighting for the respective EBRT modalities and the fractionation ranged used to treat the target population in Australian practice. The applicant expressed willingness to undertake further research to inform these assumptions more robustly.

Table 14 Additional sensitivity analyses for the economic analysis

Sensitivity analysis	Total average treatment cost (Re-188)	Total average treatment cost (EBRT – 3D megavoltage & IMRT/VMAT)	Difference
Base Case	\$5,438	\$7,086	-\$1,648
Commentary SA - multiple Re-188 treatments (base case 100% 1 Re-188 treatment)			
85% one treatment of Re-188, 15% two treatments of Re-188	\$6,254	\$7,086	-\$832
Commentary SA – including orthovoltage as an EBRT modality (base case 3D megavoltage 50%, IMRT/VMAT 50%)			
EBRT modality (orthovoltage 90%, 3D megavoltage 5%, IMRT/VMAT 5%)	\$5,438	\$1,697	\$3,742
ESC requested SA – amend electron beam (LINAC) costing (base case 3D megavoltage costed using 3D megavoltage MBS items)			
Amended electron beam cost to use 2D electron beam MBS items, retain ADAR EBRT modality (3D megavoltage 50% /IMRT/VMAT 50%)	\$5,438	\$5,854	-\$415
ESC requested multi-variate SA			
Amend electron beam cost (2D electron beam MBS items) and EBRT modality split			
EBRT split (orthovoltage 45%, electron beam 45%, IMRT/VMAT 10%)	\$5,438	\$2,325	\$3,114
EBRT split (orthovoltage 30%, electron beam 60%, IMRT/VMAT 10%)	\$5,438	\$2,443	\$2,996
EBRT split (orthovoltage 20%, electron beam 70%, IMRT/VMAT 10%)	\$5,438	\$2,521	\$2,917
Amend electron beam cost (2D electron beam MBS items), EBRT modality split (orthovoltage 20%, electron beam 70%, IMRT/VMAT 10%) and number of fractions			

6: 5 fractions	\$5,438	\$1,376	\$4,063
7: 10 fractions	\$5,438	\$1,784	\$3,654
8: 15 fractions	\$5,438	\$2,192	\$3,246
9: 20 fractions	\$5,438	\$2,601	\$2,838
10: 25 fractions	\$5,438	\$3,009	\$2,429
11: 30 fractions	\$5,438	\$3,417	\$2,021

Source: Constructed from Commentary Table 8, pg 147 of MSAC 1657 ADAR+in-line commentary and additional analyses by the Department as requested by ESC

Abbreviations: EBRT = External Beam Radiation Therapy; IMRT = Intensity-Modulated Radiation Therapy; MBS = Medicare Benefits Schedule; Re-188 = Rhenium 188; SA = sensitivity analysis; VMAT = Volumetric Modulated Arc Therapy

Commentary sensitivity analysis to account for wastage

As previously noted, one carpoule of Re-188 costs \$14,000 and can treat up to 18 cm², which could potentially treat 2 to 4 patients, each with 1 lesion sized 5-8 cm², or 6 to 12 patients, each with 1 lesion sized 1.5-3.0 cm². The ADAR estimated the cost per patient for one lesion treatment with Re-188 brachytherapy but did not include any wastage costs for the Re-188 compound. As also noted earlier, some wastage may occur and will vary depending on how efficiently lesions are batch treated. The commentary notes that the total treatment cost for Re-188 brachytherapy is likely underestimated as these wastage costs have not been included in the economic analysis. The commentary conducted a scenario analysis to assess the potential impact of wastage costs on the cost-effectiveness of Re-188 brachytherapy compared to EBRT (Table 15). In the absence of information on the feasibility to efficiently batch treat lesions and therefore the likely wastage, the commentary has assumed wastage based on only 1 lesion being treated per carpoule. The commentary acknowledges that this is an extreme scenario, but a more plausible estimate is not able to be ascertained at this time due to the lack of information on batching and wastage in the ADAR. The sensitivity analysis found that under this 'worst case scenario' of wastage, there is no longer a cost saving from Re-188 brachytherapy when compared to EBRT but instead a cost increase of \$8721 per patient where the comparator EBRT modality is the base case comparator (50% 3D megavoltage +50% IMRT/VMAT). The cost increase is \$14,111 to \$16,482 (according to different assumptions of Re-188 usage) where the comparator EBRT modality is orthovoltage 90% + 5%3D megavoltage+5% IMRT/VMAT. Note: this sensitivity analysis was conducted prior to ESC advice regarding EBRT modalities and weighting, costing for 2D electron rather than 3D megavoltage and amendment of the number of EBRT fractions.

The applicant's pre-ESC response considered the commentary sensitivity analysis to account for wastage represents an extreme and invalid comparison of highly inefficient delivery of the new intervention with perfectly efficient delivery of the comparator. The pre-ESC response stated that initial experience from the few Australian clinics currently providing Re-188 brachytherapy for keratinocyte cancer treatment suggests that batching of patients to enable rational and efficient delivery of the service is entirely feasible.

Table 15 - Scenario analysis: difference in total treatment costs including the carpoule wastage cost of the Re-188 compound, per patient

Scenario analysis	Total average treatment cost (Re-188 brachytherapy)	Total average treatment cost (EBRT)	Difference in treatment costs	Difference from the base case
Base Case (Re-188, EBRT – 3D megavoltage & IMRT/VMAT)				
Base case	\$5,438	\$7,086	-\$1,648	-
Carpoule wastage costs of the Re-188 compound included in the MBS fee for Re-188 (no batching)				
Re-188 (1 Tx) + wastage vs EBRT (3D megavoltage & IMRT/VMAT)	\$15,807	\$7,086	\$8,721	\$10,369
Re-188 (1 Tx) + wastage vs EBRT (orthovoltage 90% + 3D megavoltage /IMRT 10%)	\$15,807	\$1,696	\$14,111	\$15,759
Re-188 (85% 1 Tx , 15% 2 Tx) + wastage vs EBRT (orthovoltage 90% + 3D megavoltage /IMRT 10%)	\$18,179	\$1,696	\$16,482	\$18,130

Source: Commentary Table 12, pg 149 of MSAC 1657 ADAR+in-line commentary

Abbreviations: EBRT = External Beam Radiation Therapy; IMRT = Intensity-Modulated Radiation Therapy; Re-188 = Rhenium 188; Tx = treatment; VMAT = Volumetric Modulated Arc Therapy

14. Financial/budgetary impacts

Overview of methodology

The ADAR presented a financial impact analysis of listing Re-188 brachytherapy on the MBS, from the perspective of the MBS, over a six-year forward estimates period. The ADAR estimated the size of the uptake population (i.e., portion of eligible patients who would be treated with Re-188 brachytherapy) using an ‘internal forecast’ which estimated that 500 eligible patients would be treated with Re-188 brachytherapy in Year 1 increasing to 8,000 patients in Year 6. The ADAR assumed that all patients who are treated with Re-188 brachytherapy would otherwise have received EBRT.

Inputs and assumptions

The commentary noted that the ADAR did not provide details to justify or substantiate the ‘internal forecast’ used to estimate the uptake of Re-188 brachytherapy of 500 patients in the first year, or for the predicted growth of uptake over the following years. The commentary anticipated that the ADAR may have underestimated the population primarily because keratinocyte cancers are very common in Australia. A recent publication by Olsen et al (2022)²¹, estimated that about 2.5% of the Australian population will have a keratinocyte cancer (BCC or SCC) such that the estimated lower end of the range for incidence of keratinocyte lesions is 1,565 per 100,000 person years for BCC, and 580 per 100,000 person years for SCC. Further these tumours occur increasingly in patients 60 years and older. Although the subset of these patients that would meet the eligibility criteria for Re-188 brachy therapy is not clear. The commentary noted that it was suggested in the ratified PICO confirmation that the population

²¹ Olsen, C. M., N. Pandeya, A. C. Green, B. S. Ragaini, A. J. Venn, and D. C. Whiteman. 2022. "Keratinocyte cancer incidence in Australia: a review of population-based incidence trends and estimates of lifetime risk." *Public Health Res Pract* 32 (1). doi: 10.17061/phrp3212203.

size could be estimated using an International Registry of patients on Re-188 brachytherapy (MSAC 1657 Ratified PICO Confirmation). However, this registry was not rolled out in its entirety (as of November 2021), and the utilisation of Re-188 brachytherapy was unknown. Overall, the commentary considered that the ADAR did not provide a reliable estimate of the size of the target population that could be independently verified, and therefore, the estimated number of patients who would utilise the Re-188 brachytherapy is highly uncertain.

The applicant’s pre-MSAC response reiterated that for now the utilisation of Re-188 brachytherapy will not be based on the size of the eligible population but rather on the availability, awareness, training, acceptance, and adoption of Re-188 brachytherapy among relevant Australian clinicians.

The commentary noted that the method of costing the Re-188 brachytherapy introduced uncertainty into the financial/budgetary impact model. The ADAR calculated an “average” treatment cost of Re-188 brachytherapy and EBRT using an independent (uniform) distributions of lesion sizes and dose fractionation regimens. This distribution assumes that the lesions are equally distributed across population (34% lesions belonging to tier 1, 33% to tier 2, and 33% to tier 3); but the assumptions used in the ADAR for the financial estimates (29% of all cases belonged to tier 1, 24% to tier 2 and 47% to tier 3) did not reflect the uniform distribution assumed in the economic analysis.

The ADAR did not account for the greatest permissible gap (GPG) when calculating the MBS costs. That is, the ADAR used a cost of IMRT/VMAT dosimetry equal to \$3,401.05, as opposed to the actual value of \$3,410.05 (difference is \$9.0)—using the deduction of GPG of \$93.20 from the cost in its MBS listing (\$3,503.25). Similarly, the estimate for the cost of Re-188 brachytherapy items did not utilise the GPG. The costs to the MBS (accounting for GPG) for Re-188 brachytherapy would be \$3,420 to \$6,726 based on the size of the lesion, as opposed to the range used in the ADAR—\$2,907 to \$5,717. The GPG corrected costs of Re-188 brachytherapy are presented in the table below (Table 16).

Table 16 Cost to MBS for Re-188 brachytherapy treatment’s three tier items based on lesion size

Lesion size tier	Mid-point of the lesion size range (cm ²)	Cost	85% MBS benefit	Cost- GPG*
1	2.25	\$3,420.00	\$2,907.00	\$3,326.80
2	4	\$4,781.00	\$4,063.85	\$4,687.80
3	6.5	\$6,726.00	\$5,717.10	\$6,632.80

Source: Table 20, pg 33 of MSAC 1657 Commentary Executive Summary

Abbreviations: GPG= Greatest permissible gap considered as \$93.20 November 2022 onwards

*Applicable to the MSAC 1657 ADAR

As noted in the section 10 – Economic Evaluation, the ADAR has not addressed batching lesion treatment, wastage of the Re-188 compound or the discrepancy in the total area that one car poule of Re-188 can treat (i.e., 18 cm² or 25 cm²). It is unclear what implications this has for the financial analysis. The commentary notes it is unclear if any costs associated with wastage may be passed on as out-of-pocket expenses to the patient. These costs could be significant (potentially \$777 per cm² wastage).

Net financial implications to the MBS using EBRT (3D megavoltage & IMRT/VMAT) as comparator

The financial implications to the MBS resulting from the proposed listing of Rhenium 188 brachytherapy for treatment of non-melanoma skin cancer are summarised in Table 17. The financial implications are presented over 6 years. As noted earlier, the ADAR did not account for GPG and consequently incorrectly calculated the costs of Re-188 brachytherapy and IMRT/VMAT.

The estimated total cost to the MBS for Re-188 brachytherapy, calculated using corrected costs (by applying the GPG) was \$2,662,280 in the first year, increasing to \$42,596,480 in Year 6, with a total cost of \$114,478,040 over the six-year period— underestimated in the ADAR by approximately \$15 million. With the corrected cost of IMRT/VMAT dosimetry (using the GPG to calculate MBS benefit), the total cost of EBRT over the six years will be \$135,300,038 (underestimated in the ADAR by \$97,000). Overall, correcting the costs for Re-188 brachytherapy and IMRT/VMAT dosimetry to account for the GPG, the estimated cost-saving to the MBS was lower than that estimated in the ADAR (\$20.8 million vs \$35.8 million).

Table 17 Net financial implications of the proposed listing to the MBS - using GPG corrected MBS costs for Re-188 brachytherapy and IMRT/VMAT

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Total
Re-188 Brachytherapy							
Tier 1 items	145	290	580	1,160	1,740	2,320	6,235
Tier 2 items	120	240	480	960	1,440	1,920	5,160
Tier 3 items	235	470	940	1,880	2,820	3,760	10,105
Total items	500	1,000	2,000	4,000	6,000	8,000	21,500
Service cost*	\$2,603,630	\$5,207,260	\$10,414,520	\$20,829,040	\$31,243,560	\$41,658,080	\$111,956,090
Adjunctive cost**	\$58,650	\$117,300	\$234,600	\$469,200	\$703,800	\$938,400	\$2,521,950
Total cost	\$2,662,280	\$5,324,560	\$10,649,120	\$21,298,240	\$31,947,360	\$42,596,480	\$114,478,040
Total EBRT							
Treatments	500	1,000	2,000	4,000	6,000	8,000	21,500
Service cost	\$2,999,638	\$5,999,275	\$11,998,550	\$23,997,100	\$35,995,650	\$47,994,200	\$128,984,413
Adjunctive cost	\$146,875	\$293,750	\$587,500	\$1,175,000	\$1,762,500	\$2,350,000	\$6,315,625
Total offsets	\$3,146,513	\$6,293,025	\$12,586,050	\$25,172,100	\$37,758,150	\$50,344,200	\$135,300,038
Cost difference							
EBRT Treatments substituted with Re-188	500	1,000	2,000	4,000	6,000	8,000	21,500
Difference in service cost	-\$396,008	-\$792,015	-\$1,584,030	-\$3,168,060	-\$4,752,090	-\$6,336,120	-\$17,028,323
Difference in adjunctive cost	-\$88,225	-\$176,450	-\$352,900	-\$705,800	-\$1,058,700	-\$1,411,600	-\$3,793,675
Difference in total cost	-\$484,233	-\$968,465	-\$1,936,930	-\$3,873,860	-\$5,810,790	-\$7,747,720	-\$20,821,998

Source: Table 21, pg 34 of MSAC 1657 Commentary Executive Summary

Abbreviations: EBRT= External Beam Radiation Therapy; IMRT=Intensity-modulated radiation therapy; MBS=Medicare Benefits Scheme; VMAT=Volumetric modulated arc therapy

Combined service cost= No. of treatments X [(No. of simulation services per course x simulation cost)+ (No. of dosimetry services per course x cost of dosimetry)+ (No. of treatment services per course x No. of treatments)+ (No. of verification services per course x Cost of verification)]

Note: each treatment incurs one simulation service, one dosimetry service, 19 treatment service and 19 verification services.

Adjunctive care cost= Total treatments x [(No. of initial specialist consultations per service X Cost of initial specialist consultation)+ (No. of subsequent specialist consultations per service x cost of subsequent specialist consultation)+ (No. of wound care episodes per service x cost of wound care)]

*Service cost included total item costs for lesions 1.5-8.0 cm2- Refer to Table 1.1 on page 18 of MSAC 1657 ADAR. Item costs include cost of the Re-188 compound, general consumables, specialist, nursing, technician, capital depreciation, and overheads. Of these the cost of Re-188 compound were calculated based on the size of the lesion (Attachment MSAC 657 ADAR -Section 1 Workbook)

**Adjunctive costs include one initial and one subsequent specialist consultation and wound care episodes

ADAR sensitivity analyses

In all the one-way sensitivity analyses included in the ADAR, treatment with Re-188 brachytherapy remained cost saving to the MBS over the first six years of listing, with the magnitude of this saving varying within a range of approximately \$10 million to \$60 million (Table 22). The commentary also tested additional uptake and case distribution scenarios:

- (1) slower uptake of Re-188 brachytherapy over the next six years so that in the first year only 1% of estimated population uses Re-188 brachytherapy, increasing to 10%, 25%, 50%, 75% and finally 100% over the six year period: the assumption is based on the fact that Rhenium-SCT® brachytherapy is currently available at one site in Australia only, and may only be available to 1% of the total population in the first year of its listing on the MBS.
- (2) a uniform distribution of three types of lesions, i.e., 34% lesions belonged to tier 1, 33% lesions to tier 2, and 33% to tier 3: this assumption is based on the assumption of a “uniform distribution” of cases across the three lesion sizes as assumed in the economic analysis. The ADAR had used a distribution that assumed 29% cases presenting with Tier 1 lesions, 24% cases with tier 3 lesions and 47% cases with Tier 3 lesions in the financial analysis. The approach of using this distribution causes significant uncertainty around the overall cost of Re-188 brachytherapy and consequentially, the net financial impact.

Table 18 ADAR sensitivity analyses results – using GPG corrected MBS costs for Re-188 brachytherapy and IMRT/VMAT*

Sensitivity analysis	Base Case	Worst case		Best case	
	Value	Value	Total cost	Value	Total cost
Base case total cost over 6 years: -\$20,821,998					
Uptake (Re-188) (uptake rate%)	500 to 8,000	375 to 6,000 (100%)	-\$15,616,498	625 to 10,000 (100%)	-\$26,027,497
Comparator mix (3D megavoltage:IMRT)	50:50	75:25	\$6,058,646	25:75	-\$47,702,6410
Case distribution (Re-188) Tier 1 2 3 (%)**	29 24 47	2 18 80	\$878,383	60 34 6	-\$47,038,238
Mean fractions (EBRT)	19	14	-\$3,181,248	24	-\$38,462,748
MBS item fees (Re-188)	\$2,907 to \$5,717	\$3,634 to \$7,146	\$7,167,025	\$2,180 to \$4,288	-\$48,811,020
Additional sensitivity analyses conducted by the commentary					
Uptake (Re-188): 1% in first year increasing to 100% in 6 th year	500 to 8,000	5 to 8,000	-\$14,628,664	N/A	
UNIFORM Case distribution (Re-188) (%)	29 24 47	34 33 33	-\$28,139,523	N/A	

Source: Commentary Table 17 and 19, pg 162-164 of MSAC 1657 ADAR+in-line commentary

Abbreviations: EBRT= External Beam Radiation Therapy; GPG= Greatest Permissible Gap; IMRT=Intensity-Modulated Radiation Therapy; MBS=Medicare Benefits Scheme; Re-188=Rhenium 188; VMAT=Volumetric Modulated Arc Therapy

*As described in the preceding sections, the cost of Re-188 brachytherapy was not calculated using the GPG, rather used the 85% MBS value; Further, the cost of IMRT/VMAT dosimetry was miscalculated in MSAC 1657 ADAR, which have been corrected in this table.

**Tier 1 = lesion size 1.5 to 3cm², Tier 2 = lesion size 3.1 to 5cm² and Tier 3 = lesion size 5.1 to 8cm²

Additional sensitivity analyses on ADAR base case

Further additional sensitivity analyses, undertaken by the commentary and the department at the request of ESC, are presented in Table 19. These sensitivity analyses explore the impact of:

- inclusion of orthovoltage as one of the EBRT modalities
- amendment of the ADAR 3D megavoltage costs to 2D electron beam costs
- adjustment of the EBRT fractionation number.

Table 19 Additional sensitivity analyses results – using GPG corrected MBS costs for Re-188 brachytherapy and IMRT/VMAT*

	Year 1	Year 6	Total
ADAR base case (corrected for CPG)			
Re-188 Brachytherapy			
# services	500	8,000	21,500
Total cost	\$2,662,280	\$42,596,480	\$114,478,040
Total EBRT (3D megavoltage 50%, IMRT/VMAT 50%)			
# of EBRT services substituted	500	8,000	21,500
EBRT cost off-set	\$3,146,513	\$50,344,200	\$135,300,038
ADAR Base case - Net cost to MBS	-\$484,233	-\$7,747,720	-\$20,821,998
Commentary SA – include orthovoltage as an EBRT modality (base case 3D megavoltage 50%, IMRT/VMAT 50%)			
EBRT modality: orthovoltage 90%, 3D megavoltage 5%, IMRT/VMAT 5%			
Net cost to MBS	\$1,928,049	\$30,848,780	\$82,906,096
ESC requested SA – amend electron beam (3D megavoltage) costing			
Amended electron beam cost, retain ADAR ERBT modality split/fractions	\$63,593	\$1,017,480	\$2,734,478
ESC requested multi-variate SA			
Amend electron beam cost (2D electron beam MBS items) and EBRT modality split			
EBRT split (orthovoltage 45%, electron beam 45%, IMRT/VMAT 10%)	\$1,652,543	\$26,440,680	\$71,059,328
EBRT split (orthovoltage 30%, electron beam 60%, IMRT/VMAT 10%)	\$1,602,383	\$25,638,120	\$68,902,448
EBRT split (orthovoltage 20%, electron beam 70%, IMRT/VMAT 10%)	\$1,568,943	\$25,103,080	\$67,464,528
Amend electron beam cost (2D electron beam Mbs items), EBRT modality split (orthovoltage 20%, electron beam 70%, IMRT/VMAT 10%) and number of fractions (ADAR base case: 19 fractions)			
5 fractions	\$2,054,918	\$32,878,680	\$88,361,453
10 fractions	\$1,881,355	\$30,101,680	\$80,898,265
15 fractions	\$1,707,793	\$27,324,680	\$73,435,078
20 fractions	\$1,534,230	\$24,547,680	\$65,971,890
25 fractions	\$1,360,668	\$21,770,680	\$58,508,703
30 fractions	\$1,187,105	\$18,993,680	\$51,045,515

Source: Compiled from Commentary Table 22, pg 168 of MSAC 1657 ADAR+in-line Commentary and additional analyses by the Department as requested by ESC

Abbreviations: EBRT = External Beam Radiation Therapy; IMRT = Intensity-Modulated Radiation Therapy; MBS = Medicare Benefits Schedule; Re-188 = Rhenium 188; SA = sensitivity analysis; VMAT = Volumetric Modulated Arc Therapy

Patient out-of-pocket costs

The commentary noted that even though Re-188 brachytherapy procedures seem more expensive than EBRT (3D megavoltage and IMRT/VMAT) from an MBS perspective, the gap fee paid by patients is higher for EBRT (3D megavoltage and IMRT/VMAT) compared to Re-189 brachytherapy due to the GPG as shown in Table 20.

Given this notably low out-of-pocket costs for patients for Re-188 brachytherapy compared with EBRT, it is possible that patients may have a preference for Re-188 brachytherapy, if it is listed on the MBS even though the clinical evidence is inconclusive regarding its clinical safety and effectiveness comparative to EBRT in treating non-melanoma skin cancers in the population of interest.

Table 20 Comparison of cost to MBS and cost to patients for EBRT (3D megavoltage & IMRT/VMAT) treatment modalities and Re-188 brachytherapy

Treatment	Total cost per treatment course	Cost to MBS per treatment course	Cost to patient per treatment course
EBRT – 3D megavoltage		\$3,498.75	\$503.70
EBRT – IMRT/VMAT		\$8,499.80	\$968.25
Re-188 for Tier 1 lesions	\$3,420.00	\$3,326.80	\$93.20
Re-188 for Tier 2 lesions	\$4,781.00	\$4,687.80	\$93.20
Re-188 for Tier 3 lesions	\$6,726.00	\$6,632.80	\$93.20

Source: Adapted from Commentary Table 21, pg 166 of MSAC 1657 ADAR+in-line commentary

Abbreviations: EBRT= External Beam Radiation Therapy; GPG= Greatest Permissible Gap; IMRT=Intensity-modulated radiation therapy; MBS=Medicare Benefits Scheme; VMAT=Volumetric modulated arc therapy

15. Other relevant information

Nil.

16. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues:

- The clinical evidence for Re-188 brachytherapy is limited (k=5 small single arm studies), with four of the five studies coming from the same institution. Further, the clinical evidence was not presented in a format that would facilitate a comparative assessment of the safety and effectiveness of Re-188 brachytherapy versus the comparator external beam radiation therapy (EBRT). ESC considered the comparative safety and effectiveness of Re-188 brachytherapy versus EBRT is uncertain.
- Interim data from the ongoing prospective study of Re-188 (EPIC-Skin study) were provided. ESC noted that this study may be able to provide Australian patient specific data when completed and that this should be requested, but the study is not likely to be completed before the end of 2023.

Item descriptor and fee issues

- The item descriptors should be amended to better align with the ongoing EPIC-Skin study of Re-188 brachytherapy. That is, limit the population to patients with histologically confirmed basal cell carcinoma (BCC) as the majority of patients (80%) had (BCC) and to remove lesions located on the genitalia from the item descriptor as there were no patients with genital lesions in the EPIC-Skin study.
- The MBS item descriptor should not be limited to once per lifetime (as a patient may develop skin cancers in other areas in the future) but should not permit re-treatment of the same lesion.

- The all-inclusive single fee structure does not allow for economies of scale in patient treatment. Although it is noted the applicant is willing to work with the department and MSAC on this issue.

Further justification of the cost-components for the proposed fees is required. For example, justification of staff costs is required as these may be overestimated and clarification of whether a single carpoule of Re-188 is sufficient to treat 18cm² or 25cm². Further, the tiered lesion size approach to the MBS items and fees appears to be arbitrary and implies that batching of patients would occur, but wastage is not accounted for, and this may lead to out-of-pocket costs for patients. ESC queried whether a cost per cm² might be more appropriate, but also noted that an exact size is difficult to calculate for lesions with irregular margins.

Economic issues:

- The ADAR presented a cost-comparison which claimed Re-188 brachytherapy was cost-saving compared to EBRT. This cost-saving is highly uncertain due a number of issues with the economic analysis.
- The ADAR did not include orthovoltage (a common EBRT modality for treating skin cancer) as an EBRT comparator modality when costing EBRT. Rather the ADAR presented a weighted EBRT cost which was based on 50% 3D megavoltage (ADAR referred to as LINAC) and 50% intensity modulated radiation therapy/volumetric modulated arc therapy (IMRT/VMAT). ESC considered that orthovoltage was an appropriate comparator modality that should be included.
- The ADAR included 3D megavoltage as one of the EBRT modalities. However, ESC considered the patients in the target population would be treated with 2D electron EBRT rather than 3D megavoltage.
- There remains some uncertainty regarding the appropriate weighting for the EBRT modalities. However, ESC did not agree with the ADAR weighting (50% 3D megavoltage, 50% IMRT/VMAT) and considered 20% orthovoltage, 70% 2D electron beam and 10% VMAT/IMRT weighting may be a more appropriate representation of current clinical practice.
- The ADAR assumed the number of EBRT fractions would range between 10 – 30 with an average of 19.03 fractions. ESC noted this assumption was not aligned with clinical guidelines or literature. ESC considered a lower fractionation range with an average of 10 fractions would be more appropriate, with the lowest range of 4 fractions.
- ESC noted the ADAR used a random simulation of 100 lesion sizes and fractionations (range 10-30) across a uniform distribution to compare the average treatment costs of Re-188 brachytherapy and EBRT. The relationship between lesion size and fractionations was not well defined, making comparisons difficult. Further, the uniform distribution used for the simulation is unlikely to reflect the true clinical presentation of patients, and a normal distribution may be more appropriate.
- Sensitivity analysis exploring these issues indicate that the claimed average cost saving of \$1,648 per patient changes to an increased cost of \$2,000-\$4,000 per patient compared to EBRT.

Financial issues:

- ESC considered that the financial estimates involved substantial uncertainty relating to the size of the proposed population, uptake of Re-188, distributions of lesion sizes, number of fractions for the comparator, and percentage split of the comparator across modalities.

ESC discussion

ESC noted that the purpose of this application from Oncobeta Therapeutics Australia was to seek listing on the Medicare Benefits Schedule (MBS) of high-dose-rate brachytherapy with an epidermal isotope composed of rhenium-188 (Re-188) in patients with non-melanoma skin cancers (including basal cell and squamous cell carcinomas) who are contraindicated for surgery.

ESC noted that Re-188 is a mixed beta-gamma emitter epidermal isotope. The particles penetrate to a depth of 8–10 mm with 92% deposit within the first 3 mm. The paste used is formulated as nano-colloid containing Re-188 in a viscous polymeric matrix. When applied to the epidermis, the paste forms a sealed, dry flexible film in 10 minutes. ESC noted that it is intended to be a single treatment and the duration of treatment is calculated by a pre-determined dose.

ESC noted the various opinions in the consultation feedback. Nuclear medicine specialists supported the application. A skin cancer advocacy group supported the application, noting that the procedure reduces time away from home and work, is pain-free and non-invasive, avoids disfiguring surgery, and will reduce public waiting lists for treatment. However, several professional colleges considered that there was insufficient evidence of safety or efficacy, and the procedure may result in radiation reactions on the skin, ulceration or other complications. The procedure may not be available in rural and remote areas. ESC noted the applicant's pre-ESC response stated that availability and use of Re-188 brachytherapy will depend on training, acceptance and adoption among clinicians.

ESC discussed the three proposed MBS items. The item descriptors and fees vary by lesion size (1.5–3.0 cm², 3.1–5.0 cm², and 5.1–8.0 cm²). ESC questioned whether the item descriptors were adequately defined to prevent use beyond the intended target population and considered that the size categories were arbitrary and not justified in the application. ESC queried whether a cost per cm² might be more appropriate, but also noted that an exact size is difficult to calculate for lesions with irregular margins. ESC noted the query from the commentary about whether the MBS items should be grouped under T2–Radiation Oncology or T3–Nuclear Medicine although this is a policy issue that can be addressed closer to implementation. ESC agreed with the MBS item descriptors that had been updated to state cutaneous basal cell carcinoma (BCC) or cutaneous squamous cell carcinoma (SCC) instead of the generic term 'malignant non-melanoma', revise the diameter size to prevent overlap across the items, specify situations where surgical excision would not be possible and include service provision by radiation oncologists noting service provision by a nuclear medicine physician or radiation oncologist will depend on the relevant state or territory. ESC considered that Re-188 brachytherapy would be a Type C procedure in an outpatient setting. ESC noted the issue of whether the item descriptor should allow retreatment of lesions. ESC noted the applicant's pre-ESC response clarified that while early trials allowed multiple treatment episodes per lesion, the more recent data relates to a single episode of treatment. As such the applicant neither proposed nor anticipated that more than one instance of Re-188 brachytherapy per lesion will be required and that in rare cases of non-response, initiation of an alternative treatment approach is a more likely outcome. ESC considered that the descriptor should not be limited to once per lifetime (as a patient may develop skin cancers in other areas in the future) but should not permit re-treatment of the same lesion. ESC suggested the item descriptors could specify 'not for retreatment of previously treated lesion(s)'.

ESC noted the proposed clinical management algorithm. ESC confirmed that radiation therapy (EBRT- external beam radiation therapy) was the appropriate comparator, but noted the many different modalities for EBRT, which have different MBS fees. ESC discussed this further when discussing the economic evaluation.

ESC noted the clinical evidence base for Re-188 brachytherapy consisted of five single-arm studies that were at high risk of bias, with Castellucci (2021)²² being the study of the highest quality/most applicable evidence (with moderate to high risk of bias). The studies included small numbers of patients with varied populations, including various lesion sizes, some of which had recurred after previous treatment. Four of the five studies were from a single centre in Italy, with data collected from 2005 onwards. ESC noted the lack of long-term follow-up data. ESC noted the ADAR claimed to present a naïve indirect comparison of Re-188 brachytherapy with EBRT. However, the ADAR did not present a naïve indirect comparison, rather the ADAR presented separate narrative summaries for each of the 25 EBRT studies included in the ADAR. ESC noted the commentary tabulated some of the EBRT study data. However, ESC agreed with the commentary that the evidence was not presented in a format that would facilitate either a direct or naïve indirect comparison of Re-188 brachytherapy versus EBRT.

ESC noted safety data from the five single-arm Re-188 brachytherapy studies, ESC noted only acute toxicity data were included for the intervention, with no data reported on late toxicity. ESC also noted that there were no data on the safety of treating multiple lesions with Re-188 brachytherapy in a single patient. ESC also noted the evidence suggests that the adverse events following Re-188 brachytherapy seem mild however, ESC noted that most of the Re-188 brachytherapy studies were descriptive rather than providing detailed safety information. Based on the study by Castellucci et al. 2021, ESC noted that acute grade 3 skin toxicity occurred in 6.6% of patients treated with Re-188 brachytherapy. ESC noted the EBRT comparator studies summarised by the commentary mostly reported mild acute or late toxicity, few grade 3 acute toxicity events and no grade 3 or 4 late toxicity events.

ESC noted effectiveness data from the five single-arm Re-188 brachytherapy studies, reported 80-100% of patients had a complete response at 3–6 months. Long-term response at 24 months was 96% based on one study (Castellucci et al. 2021) with a high loss to follow up. ESC also noted the draft manuscript provided by the applicant for an unpublished single-arm effectiveness study (Tietze 2023²³) but agreed with the commentary that the data are similar in quality and relevance to the existing studies and would not alter the assessment. ESC noted the studies of the comparator (radiation therapy) reported complete response in more than 95% of patients, and cosmesis outcomes were generally excellent or good. However, ESC noted several limitations of the studies were highlighted by the commentary, including the mix of different radiation technologies using a wide variation in fractionations, evidence spanning 5 decades, and unclear lesion depth/diameters.

ESC also noted the interim statistical analysis provided by the applicant from an ongoing international phase IV open label single-arm study (the EPIC-Skin²⁴ study) with recruitment sites in Australia. The study (N=182) aims to evaluate the response to Re-188 brachytherapy in patients with non-melanoma skin cancer. 80% of patients had BCC, while 20% had SCC. Patients with lesions located on genitalia were not included in the study. The interim analysis indicated complete response in 97.2% of patients at 6 months, and the majority of patients had no pain or discomfort at 14 days. However, 24 patients experienced adverse events (such as pain, swelling and wound infection), and one patient had a serious adverse event relating to wound healing. ESC queried whether it may be appropriate to wait for these study results to be published (noting that primary completion is not expected before the end of 2023) and to request data on Australian patient outcomes. ESC also queried whether, to align with the EPIC-Skin study, the

²² Castellucci P et al. (2021). "High dose brachytherapy with non sealed (188)Re (rhenium) resin in patients with non-melanoma skin cancers (NMSCs): single center preliminary results." *Eur J Nucl Med Mol Imaging* 48 (5):1511-1521.

²³ Tietze J et al. (2023). "Topical Rhenium-188 ionizing radiation therapy exerts high efficacy in curing invasive non-melanoma skin cancer." [Unpublished manuscript].

²⁴ Rhenium-Skin Cancer Therapy (SCT) for the Treatment of Non-Melanoma Skin Cancer. (EPIC-Skin) – [NCTC 05135052](#)

MBS item descriptor should be limited to BCC and should not include lesions located on genitalia.

ESC noted that based on the evidence presented in the ADAR, the applicant proposed that Re-188 brachytherapy is likely to provide similar effectiveness and safety to fractionated regimen external beam radiation therapy. However, ESC agreed with the commentary that the available evidence does not support a conclusion of non-inferior comparative safety and effectiveness due to the low quality and low certainty of Re-188 studies and lack of comparative evidence. ESC also agreed with the commentary that a conclusion of uncertain comparative safety and effectiveness of Re-188 brachytherapy versus EBRT is more appropriate.

ESC noted the economic evaluation was a cost comparison that compared the MBS funded healthcare resources for Re-188 brachytherapy against EBRT. ESC noted that while a cost-effectiveness or cost utility analysis was proposed in the ratified PICO confirmation, the ADAR justified using the cost-comparison approach on the basis that the clinical claim had been downgraded to non-inferior safety and effectiveness and due to a limited availability of data. ESC considered that this may be appropriate due to the limited clinical evidence, differences in cost structure between the intervention and the comparator, and the absence of existing economic evaluations.

ESC noted that there was limited evidence to support the costing of Re-188 brachytherapy reported in the ADAR. ESC considered the lesion sizes that corresponded to the three MBS items to be arbitrary, but were consistent with the ratified PICO confirmation. ESC considered that further justification for each of the cost components for the proposed MBS fees was required. For example, the costs include both a technician and a nurse at the same cost. However, ESC considered justification was required to demonstrate whether both technician and nurse were required, and the cost for each. ESC also noted that in estimating costs, such as amortisation of capital equipment, the applicant had assumed 260 clinic days per year and 8 patients per day (2080 patients per year). ESC queried whether this was a robust estimate of the likely throughput in a private clinic and given the applicant's estimated utilisation (i.e., 500 patients in year 1). ESC also noted that the cost of one carpoule of Re-188 was \$14,000, but it was not clear whether one carpoule can treat up to 18 cm² (as stated in the applicant-developed assessment report [ADAR]) or up to 25 cm² (as stated in the ratified PICO confirmation). ESC noted that if one carpoule can treat an area of 25 cm², the cost across the 3 proposed items reduces from \$3,420 - \$6,720 (if assume 18 cm²) to \$2,930 - \$5,338 (if assume 25 cm²). The appropriate area (18 cm² or 25 cm²) to inform the costings should be confirmed and justified by the applicant in the pre-MSAC response. ESC noted that it would be essential to batch multiple patients for treatment from a single carpoule and queried whether this would be practical; this was confirmed in the pre-ESC response which stated that batching is feasible.

ESC noted that the costs for providing the service were calculated per patient for treatment of one lesion. ESC noted that while this all-inclusive approach may be reasonable, it did not allow for economies of scale in staff costs, or any wastage costs of Re-188 (which would vary depending on how efficiently patients can be batched). ESC noted that in estimating the cost of the Re-188 compound for each of the lesion tiers, the ADAR did not use accurate values for the midpoint of each lesion tier.

ESC considered that the relationship between lesion size and fractionation range was unclear and uncertain. This rendered uncertain the ADAR comparison between average treatment costs of Re-188 brachytherapy and EBRT which relied on a random simulation of 100 lesion sizes and fractionations (range 10-30) across a uniform distribution. ESC noted the uniform distribution assumes all patients are equally likely to have a non-melanoma skin lesion of any size which is clinically unlikely. The commentary noted that the gray (Gy) range may be a more appropriate method to establish a relationship, and this would result in fewer fractions than that proposed by the applicant. ESC noted the ADAR assumed a fractionation range of 10-30 (with an average of 19.03) for EBRT which was not aligned with clinical guidelines or literature. ESC considered a

lower fractionation range with an average of 10 fractions would be more appropriate which was used to inform additional sensitivity analyses conducted by the Department for ESC (presented in Section 11, Table 14).

ESC noted the ADAR costed the comparator (EBRT- external beam radiation therapy) as a weighted cost using a 50/50 split between 3D megavoltage and intensity modulated radiation therapy/volumetric modulated arc therapy (IMRT/VMAT). However, ESC noted that the commentary had included sensitivity analysis with a revised weighted EBRT cost which included orthovoltage as an additional EBRT modality (i.e., weighted EBRT cost assuming 90% orthovoltage, 5% 3D megavoltage and 5% IMRT/VMAT). ESC noted orthovoltage is a common EBRT modality for treating keratinocyte cancers and is significantly less costly than 3D megavoltage. Although the applicant pre-ESC response disagreed with including orthovoltage, ESC considered it was appropriate to include orthovoltage as a comparator modality in the weighted EBRT cost. However, ESC agreed that the 90% orthovoltage weighting may be high and suggested a lower weight may be more representative of current clinical practice (e.g., 20%-30% orthovoltage). ESC also considered patients in the target population would be treated with 2D electron EBRT rather than 3D megavoltage. Additional sensitivity analyses using 2D electron EBRT instead of 3D megavoltage costings and various weightings for the EBRT modalities were conducted by the department for ESC (Table 14).

ESC noted the ADAR cost comparison claimed that Re-188 brachytherapy provided a cost-saving of \$1,648 per patient compared to EBRT. However, ESC noted the additional sensitivity analyses exploring the impact of including orthovoltage, amending 3D megavoltage to 2D electron EBRT and amending the number of EBRT fractions resulted in substantial reductions in the cost of the comparator such that Re-188 brachytherapy is more expensive than EBRT. ESC acknowledged the appropriate split of EBRT modalities is uncertain, and that further expert advice would be beneficial. ESC noted the multivariate sensitivity analyses including orthovoltage as a comparator modality, amending the number of fractions and costs for 2D electron EBRT changed the economic evaluation results from an average cost saving of \$1,648 per patient to an increased cost of \$2,000-\$4,000 per patient compared to EBRT (with varying values depending on the precise split of EBRT modalities and number of fractions).

ESC noted the ADAR's financial impact analysis. ESC noted the ADAR's estimated utilisation of Re-188 brachytherapy was based on an 'internal forecast' that could not be justified or substantiated. ESC agreed with the applicant's pre-ESC response that utilisation of existing orthovoltage MBS items reflected the number of services, not the number of patients. ESC also agreed with the clarification from the pre-ESC response that the ADAR assumed all patients who receive Re-188 brachytherapy would have received EBRT in the comparator scenario, and that the ADAR was not implying Re-188 brachytherapy would 100% substitute EBRT in the target population. ESC noted that during the PICO confirmation stage (December 2021), the applicant stated intentions to establish an international registry for keratinocyte cancers, which will include an Australian component to allow a better understanding of disease epidemiology as well the utility of Re-188 brachytherapy in its treatment. However, no Australian registry data were available from the registry to inform the assessment of Re-188 brachytherapy. The pre-ESC response noted that work on the registry was initially delayed by work on the EPIC-Skin study but has now recommenced.

ESC considered that the total cost to the MBS of Re-188 brachytherapy was uncertain due to the uncertainty regarding the utilisation estimates and the method of costing Re-188 brachytherapy (including the inconsistency between the assumptions about lesion distribution used in the financials versus the economic evaluation). ESC noted the ADAR also did not account for the Greatest Permissible Gap (GPG) which was corrected by the commentary. ESC noted the issues identified for the economic analyses also impacted the financial estimates (e.g., inclusion of orthovoltage, amending the number of fractions and costs for 2D electron beam). ESC noted that while the ADAR claimed that MBS listing of Re-188 brachytherapy would save the MBS

~\$20 million over 6 years, the additional sensitivity analyses indicated that this claimed saving was highly uncertain. Further, MBS listing of Re-188 brachytherapy could in fact result in an additional cost to the MBS of up to ~\$80 million over 6 years (Table 19).

17. Applicant comments on MSAC's Public Summary Document

The applicant had no comment.

18. Further information on MSAC

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