



**Australian Government**  
**Medical Services Advisory Committee**

## **Public Summary Document**

### ***Application No. 1665 – Radiofrequency echographic multi spectrometry for bone density measurement and determination of osteopenia/osteoporosis)***

**Applicant:** Cortex Health Pty Ltd

**Date of MSAC consideration:** 28-29 July 2022

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 ultrasound radiofrequency echographic multi spectrometry (REMS) for the diagnosis of osteopenia and osteoporosis was received from Cortex Health 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 public funding of the radiofrequency echographic multispectrometry (REMS) for bone density measurement and determination of osteopenia and osteoporosis. MSAC considered the evidence presented did not demonstrate sufficient correlation of REMS with dual-energy x-ray absorptiometry (DXA). As such, MSAC queried whether there is a population for whom there is a residual clinical need for REMS and suggested that a re-application could instead identify those defined as eligible for DXA but are unable to be tested by DXA. MSAC also requested data on inter-machine variability, inter-operator variability and intra-patient variability over time.

<b>Consumer summary</b>
<p>This is an application from Cortex Health Pty Ltd requesting Medicare Benefits Schedule (MBS) listing of radiofrequency echographic multispectrometry (REMS) for the diagnosis of osteopenia and osteoporosis.</p> <p>Osteoporosis is a condition where bones become weak and fragile. For people with osteoporosis, even a minor bump or accident can cause a broken bone (called a minimal trauma fracture). Fractures due to osteoporosis can cause chronic pain, disability, loss of independence and early death. Osteopenia is a condition where bone mineral density (the</p>

### **Consumer summary**

amount of calcium and other minerals in bone) is lower than normal, but not low enough to be classified as osteoporosis. Women usually start losing bone mass earlier than men.

Dual-energy x-ray absorptiometry (DXA) is the current standard for screening and monitoring bone mineral density. Two x-ray beams with different energy levels are aimed at a patient's bones anywhere in the body but most commonly in the hips, spine and/or wrist.

Radiofrequency echographic multispectrometry is a more recent technology that uses ultrasound to scan bones in the hip and spine only.

After considering the evidence, MSAC was not convinced that REMS is as good as DXA at diagnosing osteoporosis based on low mineral density. Additionally, MSAC questioned if there was a need for REMS, as most patients would be able to have a DXA scan and those who cannot have a DXA scan (such as very obese people) would not be able to have a REMS scan either. MSAC also noted that REMS was unsuitable for some people, and that referring clinicians would need to be educated on which types of patients REMS scans would be suitable for, to lower the chance of unsuccessful scans. MSAC also noted that the quality of the REMS scans depended on the person doing it, so they would need to undergo training that is developed and accredited by relevant organisations.

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

MSAC did not support listing REMS on the MBS. MSAC considered that REMS was not as good as the current standard, DXA, and did not offer any safety or other health benefits compared to DXA. MSAC was also uncertain which patients would need to use REMS instead of DXA. If there is a small number of people for whom DXA is not possible, further evidence on how well REMS works is also needed.

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

MSAC noted that this application from Cortex Health Pty Ltd requested MBS listing of REMS for the diagnosis of osteopenia and osteoporosis. MSAC noted that listing was requested based on a claim of noninferiority (and thus cost-minimisation of MBS fees) versus DXA as the main and only comparator.

MSAC noted that the REMS technology was included on the Australian Register of Therapeutic Goods (ARTG) for use in Australia on 28 September 2020. Through its software, REMS reports standard bone mineral density (BMD) parameters for the diagnosis of osteoporosis, including a T-score.

MSAC noted that the consultation feedback including from clinical societies was generally not supportive of this application. Most of those providing comment noted that the portability of the REMS device could allow easier access to BMD scans, such as for patients in nursing homes or in rural and remote communities and some pointed to the provision of greater consumer choice. However, MSAC noted that while DXA is not as portable, it is currently provided via mobile units. MSAC also noted feedback that REMS could offer greater flexibility for patients who are unable to lie completely supine for DXA scans. However, MSAC noted that for these patients, DXA can scan other areas of the body, such as the wrist. MSAC noted that the organisations providing feedback did not consider REMS to have the same functionality as DXA because it is limited to two regions (lumbar vertebrae L1–L4 and the femoral neck), meaning REMS cannot scan other areas of the body that are measured for certain diseases specified in DXA MBS items, such as the forearm in patients with hyperparathyroidism. There was also concern that REMS cannot estimate BMD for

the total proximal femur (TPF) region of interest – one of the main sites used in DXA. MSAC noted other concerns were raised, including the discordant results between REMS and DXA, the potential for a high rate of unsuccessful scans, the inability to retrospectively review scans, and the limited data on REMS to support its utility for men and different racial populations.

Feedback also noted concerns with sufficient operator training and considered that the model of service delivery (point of care) could lead to overservicing of multiple patients at the same healthcare facility or in rural and remote settings. MSAC agreed with ESC that this potential for overservicing remained an issue.

MSAC noted that the proposed population for REMS is patients who require BMD measurement for the diagnosis or monitoring of osteoporosis and who are currently eligible for an MBS-funded DXA. MSAC noted that eligible patients would be investigated, managed and referred in the same way as for DXA scanning, and the clinical management algorithm for DXA is already well established in Australia by the Royal Australian College of General Practitioners (RACGP). However, MSAC noted in the clinical management algorithm for DXA that postmenopausal women and men over 50 years of age with minimal trauma hip or vertebral fracture do not require a DXA scan to diagnose or initiate treatment for osteoporosis.

MSAC considered the comparator of DXA to be appropriate for the current application.

Regarding comparative safety, MSAC noted that none of the studies reported significant safety issues with either REMS or DXA. However, MSAC noted that both tests have a risk of incorrect diagnosis. Regarding the risk of ionising radiation with DXA, MSAC noted that the dose associated with DXA is very low and so considered that it did not represent a significant safety concern. MSAC considered that the claim that REMS has noninferior safety compared with DXA was supported.

MSAC noted that a linked evidence approach was used to compare the effectiveness of REMS to DXA. MSAC noted that the evidence base included two key comparative cross-sectional, observational cohort studies (Cortet et al. 2021<sup>1</sup> and Di Paola et al. 2019<sup>2</sup>) and supplementary evidence consisting of three comparative studies (Amorim et al. 2021<sup>3</sup>, Nowakowska-Plaza et al. 2021<sup>4</sup> and Adami et al. 2020<sup>5</sup>). The studies were reported to have an overall low risk of bias. However, MSAC noted that there was an unclear risk of bias in patient selection for all studies. MSAC also noted that the applicant provided unpublished data for “total femur score” results from Echolight Italy (November 2017) after the applicant-developed assessment report (ADAR) submission, with results from a subgroup of patients from the Di Paola et al. 2019 key study.

MSAC noted that quality errors are possible with both DXA and REMS scans, and that the studies excluded DXA and REMS scans with quality errors from the primary analysis (referred to as the quality-checked scenario). MSAC noted that the pre-MSAC response stated that the unchecked/real life scenario is more consistent with clinical practice because the quality errors identified for REMS would not be identified in practice and so MSAC decided that the results of

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<sup>1</sup> Cortet B, Dennison E, Diez-Perez A, Locquet M, Muratore M, Nogués X et al. (2021). Radiofrequency Echographic Multi Spectrometry (REMS) for the diagnosis of osteoporosis in a European multicenter clinical context. *Bone* **143**:115786.

<sup>2</sup> Di Paola M, Gatti D, Viapiana O, Cianferotti L, Cavalli L, Caffarelli C et al. (2019). Radiofrequency echographic multispectrometry compared with dual X-ray absorptiometry for osteoporosis diagnosis on lumbar spine and femoral neck. *Osteoporosis International* **30**(2):391-402.

<sup>3</sup> Amorim DMR, Sakane EN, Maeda SS & Castro ML (2021). New technology REMS for bone evaluation compared to DXA in adult women for the osteoporosis diagnosis: a real-life experience. *Archives of Osteoporosis* **16**(1):175.

<sup>4</sup> Nowakowska-Plaza A, Wroński J, Płaza M, Sudoł-Szopińska I & Głuszko P (2021). Diagnostic agreement between radiofrequency echographic multispectrometry and dual-energy X-ray absorptiometry in the assessment of osteoporosis in a Polish group of patients. *Polish Archives of Internal Medicine* **131**(9):840-847.

<sup>5</sup> Adami G, Arioli G, Bianchi G, Brandi ML, Caffarelli C, Cianferotti L et al. (2020). Radiofrequency echographic multi spectrometry for the prediction of incident fragility fractures: a 5-year follow-up study. *Bone* **134**:115297.

this other scenario were more relevant for its deliberations. MSAC noted from the pre-MSAC response that the REMS software can still process and produce results when the scans are considered as “low-quality” (that is, the scan was not centralised), but that “invalid” scans (that is, the scan did not lock on to a region of interest) are not reported. Low-quality scans can be identified at the time of scanning with a manual review of the scan image and rectified by the operator moving the probe and re-scanning. MSAC noted the pre-MSAC response that, even with low-quality scans, there was a degree of tolerance with REMS, but considered this to be uncertain because there was no clear threshold for what would be considered acceptable or not and what would result in an erroneous scan. MSAC therefore requested evidence on the rate and any clinical implications of repeat scans before a successful scan is completed, even though unsuccessful scans could not be billed to the MBS. MSAC also noted from the pre-MSAC response that low quality scans could not be re-analysed after reviewing the REMS report for the femoral neck, but for the lumbar spine, there was an option to disregard specific vertebrae and regenerate the report and re-calculate total scores. However, MSAC noted that there was no supportive data provided on the impact of reducing the number of vertebrae included in the total score.

For comparative analytical performance (and thus effectiveness and safety based on scan results), MSAC noted that the ADAR claimed REMS is noninferior compared with DXA. MSAC noted that the two key studies reported sensitivity of between 81% - 89% and specificity of between 84.3% - 94.5% of REMS versus DXA in the more relevant unchecked/real world analysis. MSAC also noted that diagnostic concordance between REMS and DXA was low (between 76.4% and 83.4%) in this unchecked analysis. In addition, MSAC noted that:

- no noninferiority margins or minimal clinically important differences were proposed
- the TPF score was not included in the published studies; only an unvalidated and inconclusive comparison of the REMS total femur score vs the DXA TPF score was provided
- the Z-score or fragility score was not reported in any of the studies and there was no validated evidence to support use in younger populations (including premenopausal women), men, obese patients or different racial populations
- the rate of “invalid scans” was not provided; MSAC considered that invalid scans should not attract a rebate, though noted that if some patients would need a DXA after an invalid REMS scan this would result in inconvenience to the patient and providers
- the ability to generate a REMS result relies at least in part on the subjective skills of the operator, which MSAC considered is linked to uncertainties regarding the adequacy and consistency of the training of the operator, the quality assurance measures applied when the operator is using the equipment, and the sufficiency of patient throughput.

Overall, MSAC considered the conclusion of noninferior effectiveness was not supported by the evidence provided, primarily on the basis of the poor correlation in the unchecked analysis. MSAC also observed that there was no direct evidence provided for important subpopulations of the overall proposed population (including obese patients, males, younger populations and different racial populations), as the use of REMS in these subpopulations had not been evaluated.

Given this conclusion, MSAC queried whether there could be a case for reserving REMS for patients who are eligible to receive DXA according to the MBS item descriptors, but for other reasons are unable to have a DXA scan. However, MSAC considered that the criteria to determine this subpopulation were currently unclear and specifying this subpopulation might benefit from engagement by the applicant with the many professional organisations which provided consultation feedback. MSAC noted as an example that very obese people or people who cannot lie supine may not be able to have a DXA but recalled that there is the possibility of having a DXA

scan on the wrist. In addition, MSAC also recalled that for patients in nursing homes and rural and remote areas, some access to DXA through mobile units was possible. It was therefore unclear who may be eligible for, but unable to access a DXA, and therefore it was not certain what the magnitude of this outstanding unmet clinical need might be. If such a population were to be identified, then MSAC considered that the use of REMS would require reassessment of comparative safety and effectiveness with a comparator of 'no DXA', accepting that DXA could still provide a frame of reference for this new comparison. MSAC also recalled that, as the accuracy of REMS is dependent on several variables (such as the operator, the patient and possibly the machine used), MSAC advised that longitudinal data on inter-operator variability, inter-machine variability and intra-patient variability over time would need to be evaluated.

MSAC noted that the ADAR presented a fee justification to support its cost-minimisation approach, seeking to show that a REMS service would incur a fee similar to the existing MBS fee for a DXA service. MSAC noted the concerns raised by ESC regarding this approach and MSAC agreed with ESC that a more extensive assessment of cost-minimisation would have been more appropriate. The approach compared the estimated per service delivery costs for a REMS scan against the MBS fee for a DXA scan, and thus inferred there would be no expectation of a substantial difference in the provision and cost of concurrent or subsequent healthcare resources. MSAC noted the ADAR estimated the REMS per service delivery cost to be \$123.67 but that this included the capital costs for the REMS device. When the capital costs for the REMS device were excluded, the per service delivery cost for REMS was \$99.66 (similar to the DXA MBS fee of \$106.55, and the proposed MBS fee for REMS).

Regarding the inputs into the fee justification that was conducted, MSAC considered that the fee may have been underestimated due to the time required to perform the scan taking longer than the claimed 30 minutes and increased costs for the portable REMS device over the non-portable REMS device. MSAC noted that, in the pre-MSAC response, the applicant stated that the proposed time of 30 minutes is reasonable based on Australian experience, however, MSAC noted this was based on anecdotal evidence only.

In addition, MSAC considered that overall costs may have been underestimated due to transportation costs for portable devices not being accounted for and staff training costs not being included. While the cost of staff training is included in the purchase price of the machine, it did not appear to account for training of staff members that are recruited after the initial training is provided.

MSAC further considered that the type of machine and the number of scans per week per machine could affect the economic evaluation, and that if fewer scans are performed on a more expensive machine than in the ADAR then the costs would be underestimated. MSAC considered that device costs are relevant to the cost-minimisation approach.

MSAC noted that a market share approach was used to estimate the financial impact for the proposed MBS listing of REMS. MSAC considered this to be reasonable given the requested MBS listing. However, the ADAR assumed a one-for-one replacement of DXA by REMS (for initial and repeat scans) at the same MBS fee for 5 to 15% of patients (over 6 years), yielding a net cost to the MBS budget of \$0 for every year. MSAC considered this to be unreasonable as it did not account for any additional patients who may have a REMS scan who are currently unable to access DXA and the 5 to 15% uptake of REMS compared with DXA was not supported by any data (even though some utilisation data from Italy are now available). The ADAR also assumed no growth in DXA or REMS scans over time, but MSAC did not consider this appropriate as the DXA utilisation data were based on years impacted by the COVID-19 pandemic and the longer-term utilisation trend shows year-on-year growth in DXA usage, which would be expected to continue. Revisiting this assumption would be important in the context of expecting additional new patients to be tested with REMS. MSAC considered it appropriate that each service in a year is assumed

to be for a unique patient. MSAC further considered it may be appropriate to assume no impact on other health budgets, because the small increase in diagnoses of osteoporosis would be expected to increase Pharmaceutical Benefits Scheme (PBS) expenditure for osteoporosis medications to a negligible extent.

MSAC considered that general practitioners and other requesting providers would need education about which patients are unsuitable for REMS to reduce the chance of unsuccessful tests. Additionally, because successful scans are operator dependent, MSAC considered it important that operators receive (and provide evidence of) sufficient training that is developed with and accredited by relevant professional organisations. MSAC noted that the applicant is willing to work with the relevant professional societies to obtain their endorsement of its training. MSAC advised that evidence of the effectiveness and the quality assurance of the training program should be provided, as well as the learning curve involved and engagement by relevant practitioners and their professional organisations. Based on Cortet et al. 2021, MSAC considered that three days of training should be the minimum.

MSAC considered that, should it be possible to identify a population(s) that is eligible for, but unable to access a DXA, then any resubmission would need to clearly define the population where there is an unmet need. This would need to provide a reassessment of comparative safety and effectiveness with a comparator of 'no DXA', including longitudinal data on inter-operator variability, inter-machine variability and intra-patient variability over time, including linked to fracture risk, along with revised economic and financial analyses presented in accordance with the MSAC guidelines. If any direct evidence is available for the proposed population with unmet need, this should also be included.

#### **4. Background**

MSAC has not previously considered REMS for the diagnosis of osteopenia and osteoporosis. MBS listing was requested on the basis of a claim of noninferiority and cost-minimisation analysis versus DXA as the main and only comparator.

#### **5. Prerequisites to implementation of any funding advice**

The REMS technology was included on the Australian Register of Therapeutic Goods (ARTG) for use in Australia on 28 September 2020 (ARTG 344830, Table 1).

**Table 1 ARTG Certificate information**

ARTG identifier	344830
ARTG start date	28 September 2020
Product Category	Medical Device Included Class 11a
GMDN	40779
GMDN Term	Ultrasound system, bone absorptiometer
Condition	Echolight devices (EchoStation, EchoS, EchoHybrid) are all designed to accurately measure bone mineral density (BMD). These devices use patented REMS, highly specific ultrasound technology. The intended use is as a screening &/or diagnostic tool to determine BMD and give the clinician a T-Score and Z-score. The generated findings & report will determine whether the patient has normal BMD or has any degree of osteopenia or osteoporosis according to their specific readings vs matched age controls.

Source:

[https://www.ebs.tga.gov.au/servlet/xmlmillr6?dbid=ebs%2FPublicHTML%2FpdfStore.nsf&docid=3E03DC21E2CAA763CA2585F100422C5A&agid=\(PrintDetailsPublic\)&actionid=1](https://www.ebs.tga.gov.au/servlet/xmlmillr6?dbid=ebs%2FPublicHTML%2FpdfStore.nsf&docid=3E03DC21E2CAA763CA2585F100422C5A&agid=(PrintDetailsPublic)&actionid=1)

ARTG= Australian Register of Therapeutic Goods; BMD= bone mineral density; GMDN= global medical device nomenclature; REMS= radiofrequency echographic multi spectrometry.

Training of REMS' operators is required with a proposed program consisting of a 3-day training course. The applicant has not yet engaged relevant professional societies to develop and accredit a training platform for REMS. The key studies, Cortet 2021<sup>6</sup> and Di Paola 2019<sup>7</sup>, demonstrate that REMS is an operator-dependent technology (see Section 8 for further discussion). The training program used in these studies was not consistent, while Cortet 2021 considered 3 days, Di Paola considered 3 hours. The ADAR also included a supplementary study (Amorim 2021<sup>8</sup>) where all REMS operators had at least 4 months of previous clinical experience with REMS.

## 6. Proposal for public funding

The ADAR is requesting to create six new MBS items for REMS, a non-invasive ultrasound device for bone characterisation and micro-architecture assessment for the diagnosis of osteoporosis. The spectral features of the radiofrequency signals acquired during an echographic scan of the target anatomical site are used to determine the status of internal bone architecture. The lumbar vertebrae L1-L4 and the femoral neck are nominated as the pivotal sites used for a REMS scan. The pre-ESC response stated the REMS software uses the NHANES III<sup>9</sup> data but did not state if the REMS report identifies the associated population reference data used. The pre-ESC response also indicated the applicant would investigate the feasibility of adding the Australian (Geelong) database as an additional reference set.

As the ADAR proposed REMS as an alternative to DXA, the current MBS-listed investigative service for diagnosing osteoporosis, the eligible population and proposed MBS items for REMS are based on the current DXA MBS items. In the [PICO confirmation](#) for MSAC 1665, the PICO Advisory Sub-committee (PASC) and Department advised that separate items were preferred for REMS that restricted the dual claiming on REMS and DXA within the restricted time periods

<sup>6</sup> Cortet, B. et al. Radiofrequency Echographic Multi Spectrometry (REMS) for the diagnosis of osteoporosis in a European multicenter clinical context. *Bone* (2021) **143**: 115786.

<sup>7</sup> Di Paola, M. et al. Radiofrequency echographic multispectrometry compared with dual X-ray absorptiometry for osteoporosis diagnosis on lumbar spine and femoral neck. *Osteoporosis international* (2019) **30**(2): 391-402.

<sup>8</sup> Amorim, D. M. R. et al. New technology REMS for bone evaluation compared to DXA in adult women for the osteoporosis diagnosis: a real-life experience. *Archives of Osteoporosis* (2021) **16**(1): 175.

<sup>9</sup> Third National Health and Nutrition Examination Survey - <https://wwwn.cdc.gov/nchs/nhanes/nhanes3/default.aspx>

(ranging from 12 months to 5 years, depending on MBS item Table 4). The ADAR proposed item descriptors were modified in Table 2 by the Department (in blue text).

**Table 2 Department proposed new MBS items for REMS**

<p>Group D1—Miscellaneous diagnostic procedures and investigations, <i>Health Insurance (General Medical Services Table) Regulations 2021</i></p>
<p>MBS [Item Number XXXXA] (analogous to DXA item 12306)</p> <p>Bone densitometry, using radiofrequency echographic multi spectrometry, involving the measurement of 2 or more sites (including interpretation and reporting), for:</p> <p>(a) confirmation of a presumptive diagnosis of low bone mineral density made on the basis of one or more fractures occurring after minimal trauma; or</p> <p>(b) monitoring of low bone mineral density proven by bone densitometry at least 12 months previously by either dual energy x-ray absorptiometry or radiofrequency echographic multi spectrometry;</p> <p>other than a service associated with a service to which item <a href="#">12306</a>, <a href="#">12312</a>, <a href="#">12315</a>, <a href="#">12320</a>, <a href="#">12321</a>, <a href="#">12322</a>, <a href="#">XXXXB</a>, <a href="#">XXXXC</a> or <a href="#">XXXXE</a> applies.</p> <p>For any particular patient, once only in a 24 month period, <b>by using</b> either dual energy x-ray absorptiometry or radiofrequency echographic multi spectrometry</p> <p><b>Fee:</b> \$106.55 <b>Benefit:</b> 75% &amp; 85% to be applied</p>
<p>MBS [Item Number XXXXB] (analogous to DXA item 12312)</p> <p>Bone densitometry, using radiofrequency echographic multi spectrometry, involving the measurement of 2 or more sites (including interpretation and reporting) for diagnosis</p> <p>and monitoring of bone loss associated with one or more of the following:</p> <p>(a) prolonged glucocorticoid therapy;</p> <p>(b) any condition associated with excess glucocorticoid secretion;</p> <p>(c) male hypogonadism;</p> <p>(d) female hypogonadism lasting more than 6 months before the age of 45;</p> <p>other than a service associated with a service to which item <a href="#">12306</a>, <a href="#">12312</a>, <a href="#">12315</a>, <a href="#">12320</a>, <a href="#">12321</a>, <a href="#">12322</a>, <a href="#">XXXXA</a>, <a href="#">XXXXC</a> or <a href="#">XXXXE</a> applies</p> <p>For any particular patient, once only in a 12 month period <b>by using</b> either dual energy x-ray absorptiometry or radiofrequency echographic multi spectrometry</p> <p><b>Fee:</b> \$106.55 <b>Benefit:</b> 75% &amp; 85% to be applied</p>
<p>MBS [Item Number XXXXC] (analogous to DXA item 12315)</p> <p>Bone densitometry, using radiofrequency echographic multi spectrometry, involving the measurement of 2 or more sites (including interpretation and reporting) for diagnosis and monitoring of bone loss associated with one or more of the following conditions:</p> <p>(a) primary hyperparathyroidism;</p> <p>(b) chronic liver disease;</p> <p>(c) chronic renal disease;</p> <p>(d) any proven malabsorptive disorder;</p> <p>(e) rheumatoid arthritis;</p> <p>(f) any condition associated with thyroxine excess;</p> <p>other than a service associated with a service to which item <a href="#">12306</a>, <a href="#">12312</a>, <a href="#">12315</a>, <a href="#">12320</a>, <a href="#">12321</a>, <a href="#">12322</a>, <a href="#">XXXXA</a>, <a href="#">XXXXB</a> or <a href="#">XXXXE</a> applies</p>



For any particular patient, once only in a 24-month period ~~by using~~ either dual energy x-ray absorptiometry or radiofrequency echographic multi spectrometry

**Fee:** \$106.55 **Benefit:** 75% & 85% to be applied

MBS [Item Number XXXXD] (analogous to DXA item 12320)

Bone densitometry, using radiofrequency echographic multi spectrometry ~~or quantitative computed tomography~~, involving the measurement of 2 or more sites (including interpretation and reporting) for measurement of bone mineral density, if:

(a) the patient is 70 years of age or over, and

(b) either:

(i) the patient has not previously had bone densitometry; or

(ii) the T-score for the patient's bone mineral density is -1.5 or more;

other than a service associated with a service to which item 12306, 12312, 12315, 12320, 12321, 12322, XXXXA, XXXXB, XXXXC, XXXXE or XXXXF applies

For any particular patient, once only in a 5 year period ~~by using~~ either dual energy x-ray absorptiometry or radiofrequency echographic multi spectrometry or quantitative computed tomography

**Fee:** \$106.55 **Benefit:** 75% & 85% to be applied

MBS [Item Number XXXXE] (analogous to DXA item 12321)

Bone densitometry, using ~~dual energy x-ray absorptiometry or~~ radiofrequency echographic multi spectrometry, involving the measurement of 2 or more sites at least 12 months after a significant change in therapy

(including interpretation and reporting), for:

(a) established low bone mineral density; or

(b) confirming a presumptive diagnosis of low bone mineral density made on the basis of one or more fractures occurring after minimal trauma;

other than a service associated with a service to which item 12306, 12312, 12315, 12320, 12321, 12322, XXXXA, XXXXB or XXXXC applies

For any particular patient, once only in a 12 month period ~~by using~~ either dual energy x-ray absorptiometry or radiofrequency echographic multi spectrometry

**Fee:** \$106.55 **Benefit:** 75% & 85% to be applied

MBS [Item Number XXXXF] (analogous to DXA item 12322)

Bone densitometry, using ~~dual energy x-ray absorptiometry or~~ radiofrequency echographic multi spectrometry ~~or quantitative computed tomography~~, involving the measurement of 2 or more sites (including interpretation and reporting) for measurement of bone mineral density, if:

(a) the patient is 70 years of age or over; and

(b) the T-score for the patient's bone mineral density is less than -1.5 but more than -2.5;

other than a service associated with a service to which item 12306, 12312, 12315, 12320, 12321, 12322, XXXXA, XXXXB, XXXXC, XXXXD or XXXXE applies

For any particular patient, once only in a 2 year period ~~by using~~ either dual energy x-ray absorptiometry or radiofrequency echographic multi spectrometry or quantitative computed tomography

**Fee:** \$106.55 **Benefit:** 75% & 85% to be applied

Consistent with requirements included for the DXA items, the Department proposed the following requirements to claim REMS MBS items XXXXA to XXXXF:

- (1) It is intended that items XXXXA to XXXXF must be performed by a:
  - (a) specialist or consultant physician who is appropriately qualified to perform the service and to whom the patient has been referred by another medical practitioner; or

- (b) another person:
  - i. who is not a medical practitioner, and
  - ii. who provides the service, in accordance with accepted medical practice, and
  - iii. who is appropriately qualified to perform the service; and
  - iv. who is under the supervision of a specialist or consultant physician responsible for the service;
- (c) the specialist or consultant physician who is responsible for the service is to perform the interpretation and reporting for the service; and
- (d) the specialist or consultant physician who is supervising the service is available to monitor and influence the conduct and diagnostic quality of the examination and, if necessary, to attend on the patient personally.

The ADAR proposed the following amendments to the MBS explanatory notes to account for specific REMS requirements:

- Operator training requirement modified.
- Reference to Quantitative Computed Tomography (qCT) removed, as this is not referred to in analogous REMS items.
- Reference to REMS use at sites other than lumbar spine or proximal femur removed.

The proposed explanatory notes (Table 3) are analogous to those for DXA<sup>10</sup>, modified for REMS.

**Table 3 The applicant proposed explanatory notes for REMS MBS items**

MBS code	Definitions	Professional supervision and interpretation and reporting	Referrals
12306 to 12322	An examination under any of these items covers the measurement of 2 or more sites, interpretation and provision of a report; all performed by a specialist or consultant physician in the practice of his or her specialty. Two or more sites must include the measurement of bone density of the lumbar spine and proximal femur.	The interpretation and report for all bone densitometry services must be provided by a specialist or consultant physician. Items 12306, 12312, 12315, 12321 and Items 12320 and 12322 (when performed using dual energy x-ray absorptiometry) must be performed by a: (a) specialist or consultant physician; or (b) person who has completed an accredited REMS training course, and who is under the supervision of a specialist or consultant physician.	Bone densitometry services are available on the basis of referral by a medical practitioner to a specialist or consultant physician. However, providers of bone densitometry to whom a patient is referred for management may determine that a bone densitometry service is required in line with the provisions of Items 12306, 12312, 12315, 12320, 12321 and 12322.
12306			For Item 12306 the referral should specify the indication for the test, namely: (a) 1 or more fractures occurring after minimal trauma; or (b) monitoring of low bone mineral density proven by previous bone densitometry.
12312			(a) 'Prolonged glucocorticoid therapy' is defined as the commencement of a dosage of

<sup>10</sup> Available at:  
<http://www9.health.gov.au/mbs/fullDisplay.cfm?type=note&q=DN.1.18&qt=noteID&criteria=bone%20mineral%20density>  
 (accessed February 2022)

MBS code	Definitions	Professional supervision and interpretation and reporting	Referrals
			<p>inhaled glucocorticoid equivalent to or greater than 800 micrograms beclomethasone dipropionate or budesonide per day; or</p> <p>(b) a supraphysiological glucocorticoid dosage equivalent to or greater than 7.5 mg prednisolone in an adult taken orally per day; for a period anticipated to last for at least 4 months.</p> <p>Glucocorticoid therapy must be contemporaneous with the current scan. Patients no longer on steroids would not qualify for benefits. A malabsorptive disorder is defined as one or more of the following:</p> <ul style="list-style-type: none"> <li>(a) Male hypogonadism is defined as serum testosterone levels below the age matched normal range.</li> <li>(b) Female hypogonadism is defined as serum oestrogen levels below the age matched normal range.</li> </ul>
12315			<p>For Item 12315 the referral should specify the indication for the test, namely:</p> <ul style="list-style-type: none"> <li>(a) primary hyperparathyroidism;</li> <li>(b) chronic liver disease;</li> <li>(c) chronic renal disease;</li> <li>(d) proven malabsorptive disorders;</li> <li>(e) rheumatoid arthritis; or</li> <li>(f) conditions associated with thyroxine excess:</li> </ul> <ul style="list-style-type: none"> <li>(a) malabsorption of fat, defined as faecal fat estimated at greater than 18 gm per 72 hours on a normal fat diet; or</li> <li>(b) bowel disease with presumptive vitamin D malabsorption as indicated by a sub-normal circulating 25-hydroxyvitamin D level; or</li> <li>(c) histologically proven Coeliac disease.</li> </ul>
12320	<p>Patients assessed as having a normal study or mild osteopenia as measured by a t-score down to -1.5 are eligible for one scan every 5 years (item 12320). Items 12320 and 12322 enable the payment of a Medicare benefit for a bone densitometry service performed on a patient aged 70 years or over. Patients 70 years and over are eligible for an initial screening study.</p>		
12321	<p>Item 12321 is intended to allow for bone mineral density measurement following a significant change in therapy - e.g. a change in the class of drugs - rather than for a change in the dosage regimen.</p>		
12322	<p>Patients with moderate to marked osteopenia as measured by a T-score of -1.5 to -2.5 are eligible for one scan every two years (item 12322). Items 12320 and 12322 enable the payment of a Medicare benefit for a bone densitometry service performed on a</p>		

MBS code	Definitions	Professional supervision and interpretation and reporting	Referrals
	patient aged 70 years or over. Patients 70 years and over are eligible for an initial screening study.		

Source: p.26-38 in the MSAC 1665 ADAR

MBS= Medicare Benefit Schedule; REMS= radiofrequency echographic multi spectrometry.

The ADAR proposed an MBS fee of \$106.55 for REMS, equivalent to the MBS fee for DXA. The number of services allowed per patient per year was dependent on the population being studied and was consistent with the current listing for DXA. The number of services allowed for each DXA MBS item is presented in Table 4.

No robust evidence was provided to support the use of REMS in males, pre-menopausal women, and certain conditions including male hypogonadism, chronic liver disease, hyperparathyroidism and secondary osteoporosis. The ADAR provided supplementary evidence in some of these populations that were not well represented in the key studies by Cortet 2021 and Di Paola 2019.

**Table 4 Services allowed per year for existing DXA scan MBS items**

	MBS item					
	12306	12312	12315	12320	12321	12322
One service allowed per patient in:	24 months	12 months	24 months	5 years	12 months	2 years
MBS approved populations	Previously identified low BMD diagnosed based on fractures following minimal trauma or monitoring of low BMD proven by densitometry at least 12 months previously.	Bone loss associated with prolonged glucocorticoid therapy, any condition associated with excess glucocorticoid secretion, male hypogonadism, female hypogonadism lasting more than 6 months before the age of 45.	Bone loss associated with primary hyperparathyroidism, chronic liver disease, chronic renal disease, any proven malabsorptive disorder, rheumatoid arthritis, any condition associated with thyroxine excess.	Patient aged 70 years of age or over who has not previously had bone densitometry or the t-score for the patient's BMD is -1.5 or more.	Established low BMD or confirming a presumptive diagnosis of BMD made on the basis of 1 or more fractures occurring after minimal trauma.	Patient is over 70 years of age and the t-score is less than -1.5 but more than -2.5

BMD= bone mineral density, DXA= dual energy x-ray absorptiometry, MBS= Medicare Benefits Schedule.

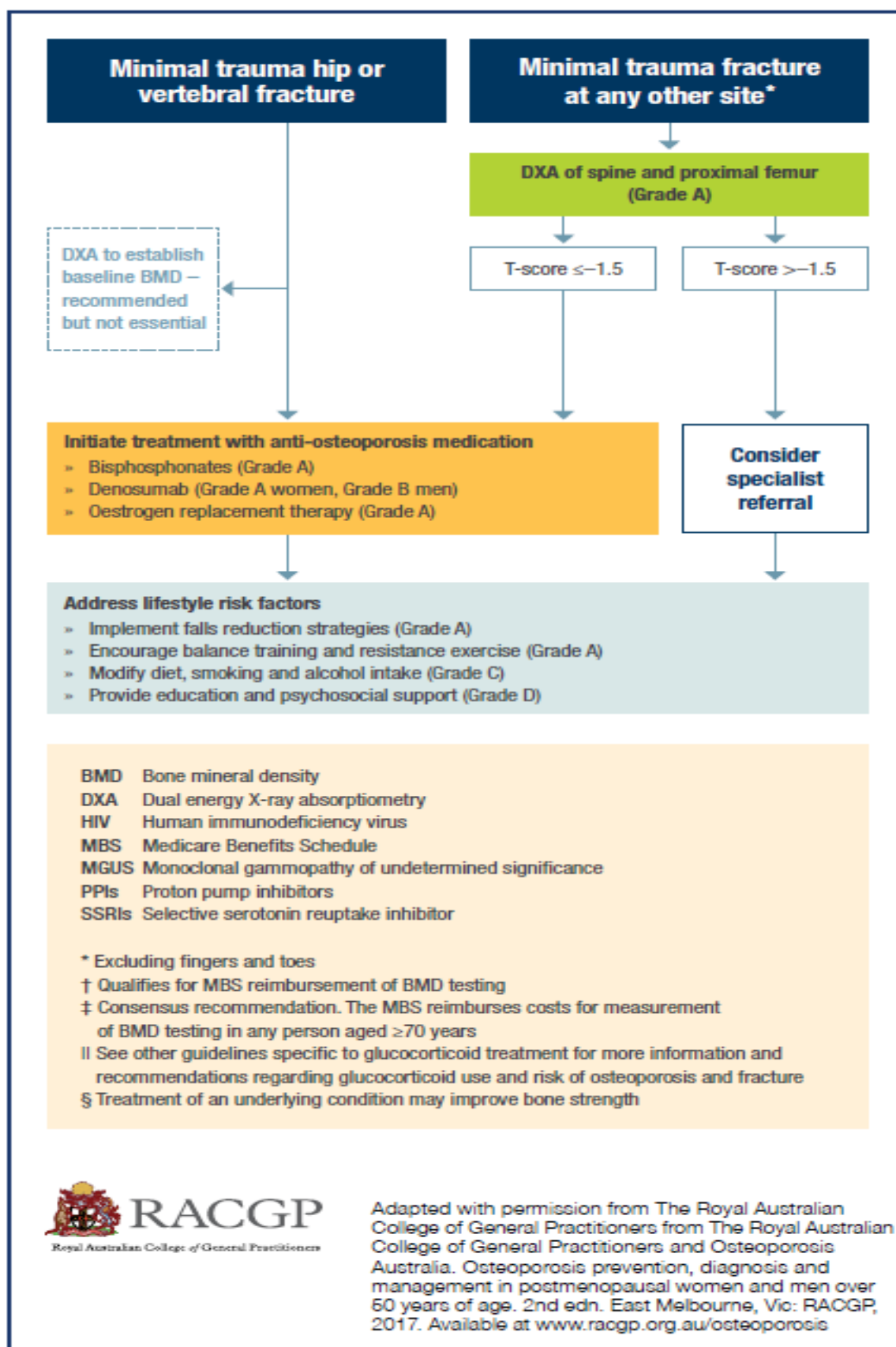
Source: MBS online (<http://www.mbsonline.gov.au/internet/mbsonline/publishing.nsf/Content/Home>).

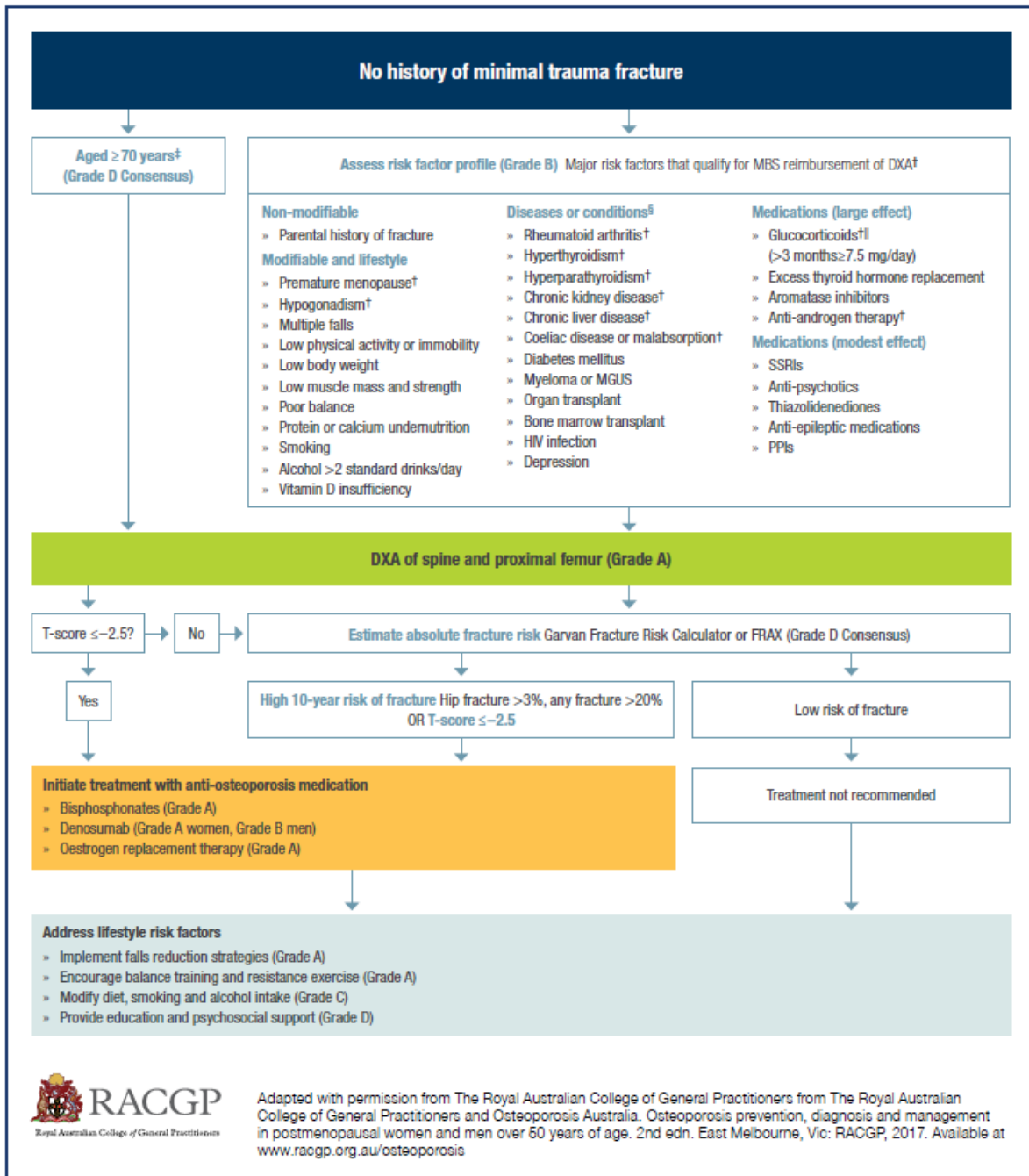
## 7. Population

The proposed population are patients who require a BMD measurement for the diagnosis or monitoring of osteoporosis and who are currently eligible for an MBS funded DXA. Prior to being considered eligible for REMS, patients would be investigated, managed and referred in the same way as they currently are for DXA scanning (see the clinical algorithm depicted in Figure 1). It is

expected that REMS would be an alternative to DXA for the diagnosis of osteoporosis in the following populations:

- previously identified low BMD diagnosed based on fractures following minimal trauma or monitoring of low BMD proven by densitometry at least 12 months previously (MBS item 12306)
- bone loss associated with prolonged glucocorticoid therapy, any condition associated with excess glucocorticoid secretion, male hypogonadism, female hypogonadism lasting more than 6 months before the age of 45 (MBS item 12312)
- bone loss associated with primary hyperparathyroidism, chronic liver disease, chronic renal disease, any proven malabsorptive disorder, rheumatoid arthritis, any condition associated with thyroxine excess (MBS item 12315)
- patient aged 70 years of age or over who has not previously had bone densitometry or the T-score for the patient's BMD is -1.5 or more (MBS item 12320)
- established low BMD or confirming a presumptive diagnosis of BMD made on the basis of 1 or more fractures occurring after minimal trauma (MBS item 12321)
- patient is over 70 years of age and the T-score is less than -1.5 but more than -2.5 (MBS item 12322).





T-score ≤ -2.5?

No → Estimate absolute fracture risk Garvan Fracture Risk Calculator or FRAX (Grade D Consensus)

Yes

**High 10-year risk of fracture** Hip fracture >3%, any fracture >20%  
OR T-score ≤ -2.5

Low risk of fracture

**Initiate treatment with anti-osteoporosis medication**

- » Bisphosphonates (Grade A)
- » Denosumab (Grade A women, Grade B men)
- » Oestrogen replacement therapy (Grade A)

Treatment not recommended

**Address lifestyle risk factors**

- » Implement falls reduction strategies (Grade A)
- » Encourage balance training and resistance exercise (Grade A)
- » Modify diet, smoking and alcohol intake (Grade C)
- » Provide education and psychosocial support (Grade D)



Royal Australian College of General Practitioners

Adapted with permission from The Royal Australian College of General Practitioners from The Royal Australian College of General Practitioners and Osteoporosis Australia. Osteoporosis prevention, diagnosis and management in postmenopausal women and men over 60 years of age. 2nd edn. East Melbourne, Vic: RACGP, 2017. Available at [www.racgp.org.au/osteoporosis](http://www.racgp.org.au/osteoporosis)

**Figure 1 Proposed clinical management algorithm for osteoporosis risk assessment, diagnosis and management: for DXA and for REMS**

Source: MSAC 1665 PICO Confirmation Figure 4, sourced from [February 2021 Healthy Bones Position Statement on the Management of Osteoporosis](#)

## 8. Comparator

The ADAR nominated DXA as the main and only comparator. This is consistent with the ratified [PICO confirmation](#) (p.12, MSAC 1665 PICO Confirmation).

DXA is a way of measuring BMD using spectral imaging. In a DXA scan, two x-ray beams, with different energy levels are aimed at a patient's bones (usually the lumbar spine and hip). When soft tissue absorption is subtracted out, the BMD can be determined from the absorption of each

beam by bone. DXA scans are subsidised under the MBS for eligible patients. The MBS items that can be claimed for DXA services are: 12306, 12312, 12315, 12320, 12321 and 12322.

The following arguments were provided by the ADAR to justify DXA as the main comparator:

- DXA is the most widely used and thoroughly studied bone density measurement technology used in Australia for the diagnosis of osteoporosis/osteopenia. Furthermore, DXA is the only diagnostic tool recommended by the Royal Australian College of General Practitioners (RACGP) for the assessment, diagnosis and management of osteoporosis.
- DXA is currently funded via the MBS.

DXA can be used to scan and measure BMD at other sites (e.g. wrist, forearm, heel) which cannot be assessed by REMS. Therefore, a comparison of DXA and REMS at these sites was not able to be assessed. This has implications for certain populations including those with hyperparathyroidism where the effects of increased bone turnover leading to low BMD, and increased fracture are mainly seen in the distal forearm (rich in cortical bone). The pre-ESC response claimed that this was likely to be a rare request and noted that the most appropriate scan would be DXA for these patients.

## 9. Summary of public consultation input

Consultation input was received from one (1) individual and eight (8) organisations:

- Australian and New Zealand Bone and Mineral Society (ANZBMS)
- Australian Diagnostic Imaging Association (ADIA)
- Australian Society of Medical Imaging and Radiation Therapy (ASMIRT)
- Australasian Association of Nuclear Medicine Specialists (AANMS)
- Australasian Sonographers Association (ASA)
- Healthy Bones Australia (HBA)
- Royal Australian and New Zealand College of Radiologists (RANZCR)
- Royal Australian College of General Practitioners (RACGP).

Most organisations were not supportive of the application; however, the Australasian Sonographers Association and the individual supported the application. Organisations not supportive of the application however noted that REMS measurement of BMD may have potential use in settings where patients would not be able to easily access DXA.

### Benefits suggested by the consultation

Most responses noted that the portability of the REMS device would allow easier access to BMD scans, such as for patients in nursing homes or rural and remote communities. It was also noted that REMS is radiation free, but levels of radiation associated with a DXA scan are very low.

The individual, a nurse educator, noted that REMS could offer greater flexibility for patients who are unable to lie completely supine for DXA scans, and would also provide greater consumer choice. It was also noted that test accuracy is important for consumer confidence because taking osteoporosis treatment is dictated by the BMD result, and the individual stated that REMS would also have the potential for greater accuracy.



### Disadvantages suggested by the consultation

Organisations considered DXA the gold standard for BMD assessment and did not consider that the REMS technology had the same functionality as DXA. They noted the following disadvantages for the REMS technology, including:

- Discordant results between REMS and DXA scans in lumbar spine and femoral neck had been found in a significant percentage of patients. This may lead to diagnostic confusion, which will be particularly difficult for patients who have previously received a DXA and could result in a requirement for additional scans (with an out-of-pocket cost to patients).
- REMS may not obtain an adequate scan at the spine or hip in a significant number of subjects, especially in overweight patients, and the rate of unsuccessful scans may exceed 15% based on published studies.
- REMS scans are limited to two regions, being lumbar vertebrae L1-L4 and the femoral neck. A major limitation of REMS is therefore the inability to estimate BMD for TPF region of interest, one of the main sites used in DXA, and the recommended 'Gold standard' site for monitoring the proximal femur. The validity of the diagnostic claims for REMS was queried given the studies have excluded TPF.
- REMS is not currently able to estimate BMD for the forearm (e.g. distal radius), a site commonly scanned using DXA to estimate BMD in patients with hyperparathyroidism.
- There is limited data on REMS to support its utility for men (noting the potential for more unsuccessful scans due to larger abdominal thickness for many men), for monitoring response to therapy and fracture risk, and for many of the conditions indicated, such as glucocorticoid induced osteoporosis and male hypogonadism.
- There is limited data for the REMS method on reference ranges used to calculate T- and Z-scores with no ability to change reference ranges in different racial populations with potential limitations in a multiracial society.
- DXA scans can be reviewed and retrospectively reanalysed, while REMS scans have no mechanism for retrospective review and cannot assess the accuracy of the scan after its acquisition.
- REMS scans may be less acceptable to patients, requiring the use of ultrasound gel on the abdomen and groin, with subsequent clean-up required at scan completion.
- In addition, concerns were raised that it may take longer to perform a REMS scan than a DXA scan, and there may be a higher operator cost for REMS scans due to proposed staff and reduced patient throughput.
- ADIA noted that REMS is not performed in a radiology clinic and therefore the multimodality follow-ups which are often required for these cases, such as thoracic spine x-rays for vertebral height loss, are not immediately available.
- RANZCR also considered that the model of service delivery (point of care) would lead to over-servicing of multiple patients at the same health care facility.
- The Australasian Sonographers Association noted that while DXA is undertaken by radiographers, sonographers may have a role in performing REMS.
- Ultrasound investigations are very user dependent, noting challenges with repeatability and operator dependence, and consultation feedback expressed concern whether the training was sufficient. Additionally, it was noted that there was a lack of clarity on who will accredit the REMS training program, who will be claiming the REMS MBS items and that the item descriptors did not include sufficient detail on what constitutes "appropriately qualified" REMS technicians.

- ADIA raised that there is insufficient information on which practitioner takes responsibility for the service and which clinician will be able to bill the service.
- ADIA raised that DXA currently forms part of a comprehensive diagnostic imaging service with established follow-up pathways and was concerned that the same has not been described for REMS, creating a risk that REMS will be done in isolation leading to patients being missed or not followed up.

## 10. Characteristics of the evidence base

There is no evidence for direct test to health outcomes for REMS. Instead, the ADAR used a linked evidence assessment framework truncated at test accuracy to compare REMS with DXA. This approach was appropriate as the ADAR proposed that REMS will replace DXA scans and result in noninferior per patient health outcomes. The ADAR included two key comparative cohort studies (Cortet 2021 and Di Paola 2019) along with supplementary evidence consisting of three comparative studies (Amorim 2021, Nowakowska-Plaza 2021<sup>11</sup> and Adami 2020<sup>12</sup>). In addition, the applicant provided unpublished data for 'total femur score' results from EchoLight Italy November 2017 post-ADAR submission, these patients were a subgroup from the Di Paola 2019 key study. The ADAR also presented supplementary data for other populations based on six conference abstracts (Ciardo2021<sup>13</sup>, Cortet 2021<sup>14</sup>, Cortet 2021<sup>15</sup>, Cavalli 2019<sup>16</sup>, Tomai 2019<sup>17</sup> and Decianu 2018<sup>18</sup>) and one cross-sectional non-comparative study (Conradie 2014<sup>19</sup>). These supplementary data were not relied on for evidence of test accuracy. None of the studies reported safety results.

The ADAR excluded studies if they were non-comparative or if the outcomes were reported for one site only (e.g. lumbar site and not femoral) and if test accuracy (i.e. sensitivity/specificity)

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<sup>11</sup> Nowakowska-Plaza, A., J. et al. Diagnostic agreement between radiofrequency echographic multispectrometry and dual-energy X-ray absorptiometry in the assessment of osteoporosis in a Polish group of patients. *Polish Archives of Internal Medicine* (2021) **131**(9): 840-847.

<sup>12</sup> Adami, G., D. et al. Radiofrequency echographic multi spectrometry for the prediction of incident fragility fractures: A 5-year follow-up study. *Bone* (2020) **134**: 115297.

<sup>13</sup> [Conference Abstract] Ciardo, D., P. et al. REMS Technology for the Assessment of Bone Health in a Male Population. *Arthritis Rheumatol* (2021) **73**

<sup>14</sup> [Conference Abstract] Cortet, B., E. et al. Diagnosis of osteoporosis using Radiofrequency Echographic Multi Spectrometry (REMS) at lumbar spine in patients with different Body Mass Index. *European E-Congress of Rheumatology (EULAR), 2-5 June 2021*.

<sup>15</sup> [Conference Abstract] Cortet, B., E. et al. Radiofrequency Echographic Multi Spectrometry (REMS) for the diagnosis of osteoporosis in patients with different body mass index. *Virtual World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (WCO-IOF-ESCEO), 26-29 August 2021*.

<sup>16</sup> [Conference Abstract] Cavalli, L., B. et al. "Screening precoce dell'osteoporosi: valutazione di soggetti giovani mediante la tecnica non invasiva REMS. *Reumatismo* (2019) **71**: EP0424.

<sup>17</sup> [Conference Abstract] Tomai Pitinca, M. D. et al. Bone mineral density measured by the radio frequency echographic multispectrometry (REMS) technique in patients in long term steroid treatment with and without fracture. *Osteoporosis International* (2019) **30**(SUPPL 2): S643.

<sup>18</sup> [Conference Abstract] Decianu, R., I. A. et al. Femoral neck bone mineral density evaluation using a quantitative ultrasound method (echolight) in a group of patients with rheumatoid arthritis. *Clinical and Experimental Rheumatology* (2018) **36**(Supplement 109): S47-S48.

<sup>19</sup> Conradie, M., M. M. et al. Bone density in black and white South African women: contribution of ethnicity, body weight and lifestyle. *Arch Osteoporos* (2014) **9**: 193.

were not reported. Given the paucity of the data in populations different from post-menopausal women, the exclusion criteria may not be appropriate. For example, Casciaro et al. (2016)<sup>20</sup> was excluded on the basis of only reporting lumbar spine and not reporting test accuracy such as sensitivity and specificity (diagnostic agreement for osteoporosis/osteopenia/healthy was reported). However, this study included overweight individuals with a BMI  $\geq 25\text{kg/m}^2$  (and possibly obese patients) aged 45-80 years. In addition, it was noted that the ADAR had initially excluded a conference abstract (Ciardo 2021) on the basis of “Inappropriate indication or patient population or outcomes” but then included it as supplementary data to support the use on REMS in males. It is possible that other studies initially excluded by the ADAR could have provided some useful data in certain patient groups within the proposed eligible population for which there is no evidence.

### **Key evidence for test accuracy**

The primary outcome of diagnostic accuracy and diagnostic concordance relied on two key studies, Cortet 2021 and Di Paola 2019. These two studies were multi-centre, cross-sectional observational cohort, prospective studies (Table 6).

The patients in the studies were not restricted to the specific proposed MBS criteria. The studies included mainly post-menopausal female patients. The ADAR claimed this provided a relatively homogenous population that could be readily recruited into these large studies, representing the majority of patients that would be routinely referred for DXA investigations. The commentary noted this seemed reasonable and largely consistent with the Australian population who receive DXA. However, given the lack of data to support the use of REMS for all the MBS items for which listing is sought, it cannot be assumed that the noninferiority claim will be met in all patient groups within the proposed eligible population. Therefore, the issue of the clinical evidence not matching the current MBS items remains an issue, for example patients with hyperparathyroidism.

### **Exclusion of REMS scans with quality errors**

The key studies (Cortet 2021 and Di Paola 2019) and ADAR presented the comparative diagnostic accuracy of REMS versus DXA using two scenarios: (1) primary analysis which represented a ‘quality-checked scenario’ where scans with quality errors (referred to as ‘erroneous’ scans in the ADAR) were excluded; and (2) supplementary analysis referred to as the ‘unchecked/real life scenario’ where REMS scans with quality errors were added back in (i.e. REMS scans with quality errors were not excluded while DXA scans with quality errors were excluded).

In both studies, two experienced operators checked all the medical reports along with the REMS datasets in an independent double-blind manner in order to identify possible acquisition errors that could result in inappropriate diagnostic classifications. Similarly, these operators identified DXA errors. The definition of a quality error was the same in Cortet 2021 and Di Paola 2019 as follows:

- DXA errors: typically associated with inaccurate patient positioning, analysis pitfalls (e.g. incorrect placement of analysis boxes in the image), presence of artifacts or mistakes in the registration of demographic characteristics.
- REMS errors: typically associated with incorrect settings of acquisition parameters (e.g. suboptimal settings of transducer focus, and/or scan depth), or with incomplete

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<sup>20</sup> Casciaro, S., P. et al. An Advanced Quantitative Echosound Methodology for Femoral Neck Densitometry. *Ultrasound in Medicine and Biology* (2016) **42**(6): 1337-1356.

adherence to the indications provided by the software and/or user guide (e.g. missing or delayed movement from a given vertebra to the subsequent one).

The commentary noted that a proportion of DXA scans identified with a quality error could be re-analysed with some not requiring their exclusion. As such in Di Paola 2019, DXA scans with quality errors that could be corrected were included in the primary analysis (this was not correctly articulated in the ADAR), however this was not done in Cortet 2021 as presented in Table 5. However, in the pre-MSAC response it was clarified that femoral REMS scans with quality errors cannot be re-analysed in practice, though it is possible that vertebra can be excluded from analysis and the remaining vertebral REMS scans can then be re-analysed. The commentary noted that there is no information available to understand the impact of the unidentified REMS scans with quality errors, mainly whether it can lead to over/under-estimation of BMD, hence osteoporosis diagnoses. The differences in training and rate of quality check errors identified in REMS scans between Cortet 2021 and Di Paola 2019, highlight the fact that this may be operator dependent – training is therefore essential to reduce the rate of REMS scans with quality errors which will not be identified in practice. The pre-MSAC response did not address this issue but reiterated that interpreting the results of REMS are operator independent; there is no ambiguity or operator interpretation required and the software does all the calculations from the retrieved scans.

The ADAR noted that by excluding ‘scans with quality errors’ from the primary analysis there may be a risk of bias for patient flow and timing based on the QUADAS-2 checklist. As the supplementary ‘real-world’ analysis re-included excluded REMS scans with quality errors but did not re-include excluded DXA scans with quality errors, the risk of bias was reduced rather than eliminated and, as a consequence, the risk of flow and timing was considered by the evaluation to be ‘unclear’ rather than ‘low’ as suggested by the ADAR.

The reasons why REMS scans were excluded and the magnitude of excluded scans are summarised in Table 5.

**Table 5 Reasons for exclusion of REMS and DXA scans in the two key studies**

	Di Paola 2019				Cortet 2021			
	Lumbar spine		Femoral neck		Lumbar spine		Femoral neck	
	N	%	N	%	n	%	n	%
<b>Scans conducted</b>	<b>1553</b>		<b>1637</b>		<b>4245</b>		<b>4271</b>	
<u>Quality check of DXA scans</u>								
Initial DXA scans identified with errors	374	24%	276	17%	408	10%	340	8%
Re-analysed DXA scans	296	19%	217	13%	0	0%	0	0%
- Wrong data analysis	210	14%	215	13%				
- Correctable artifacts	84	5%	0	0%				
- Data input mistakes	2	0%	2	0%				
<b>Excluded DXA scans with errors</b>	<b>78</b>	<b>5%</b>	<b>59</b>	<b>4%</b>	<b>408</b>	<b>10%</b>	<b>340</b>	<b>8%</b>
- Inaccurate patient positioning	78	5%	51	3%				
- Uncorrectable artifacts	0	0%	8	0%				
<u>Quality check of REMS scans</u>								
Initial REMS scans identified with errors	340	22%	239	15%	373	9%	323	8%
Recovered REMS scans	60	4%	34	2%	0	0%	0	0%
- Acceptable focus selection	42	3%	27	2%				
- Acceptable scan depth selection	18	1%	7	0%				
<b>Excluded REMS scans with errors</b>	<b>280</b>	<b>18%</b>	<b>205</b>	<b>13%</b>	<b>373</b>	<b>9%</b>	<b>323</b>	<b>8%</b>
- Wrong focus selection	185	12%	165	10%				
- Wrong scan depth selection	92	6%	40	2%				
- No adherence to scan procedure	3	0%	0	0%				
<b>Total scans included in primary 'quality checked' analysis<sup>a</sup></b>	<b>1195</b>	<b>77%</b>	<b>1373</b>	<b>84%</b>	<b>3464</b>	<b>82%</b>	<b>3608</b>	<b>84%</b>
<b>Total scans included in supplementary 'real-world' analysis<sup>b</sup></b>	<b>1475</b>	<b>95%</b>	<b>1578</b>	<b>96%</b>	<b>3837</b>	<b>90%</b>	<b>3931</b>	<b>92%</b>

DXA= dual energy x-ray absorptiometry; REMS= radiofrequency echographic multi spectrometry.

Source: Cortet 2021 and Di Paola 2019.

Notes:

a Total scans included in primary 'quality checked' analysis = Total scans - excluded DXA scans - excluded REMS scans

b Total scans included in supplementary 'real-world' analysis = Total scans - excluded DXA scans

In addition to Cortet 2021 and Di Paola 2019, the applicant provided a third unpublished report to address the claim that the REMS total femur score (a composite of the femoral neck and upper trochanter) can be considered equivalent to the DXA total proximal femur measurement. This unpublished report (2017 EchoLight Italy Evaluation Report) followed the same approach of excluding scans with quality errors but only present a quality check scenario (i.e. did not present a real-world scenario where REMS scans with quality errors were included in the analysis). This report excluded 31.5% of scans (16.9% DXA scans and 14.6% REMS scans with quality errors) from the analysis leading to an 'unclear' risk of bias for patient flow and timing. The pre-ESC response provided a comparison of REMS total femur score versus DXA TPF where all scans were included (REMS and DXA scans with quality errors were not excluded). However, this analysis was not consistent with how the data was analysed in the unchecked real-life scenario in the published studies (i.e., where REMS scans with quality errors were not excluded while DXA scans with quality errors were excluded) and therefore not informative.

The commentary highlighted that the ADAR did not address whether or not REMS scans with quality errors would be identified in practice, the applicability of the results from the two

scenarios, and the implications in terms of the rate and type of repeat testing if REMS scans with quality errors are in fact identified in practice. The pre-MSAC response clarified that quality errors could be possible (for example due to the scan not being centralised over the region of interest) but noted that the software could still produce a result using these lower-quality scans. It was stated that when interpreting results from a completed scan, each REMS scan report includes a visual representation of the positioning of the region of interest in the highlighted scan on the last page of the report in which the operator or clinician can manually check the quality of the images. The pre-MSAC response also noted that invalid scans were also possible, in the situation where the region of interest was not captured at all and in these circumstances, a null or invalid reading would be returned to the operator with no results generated, and this would allow the operator to re-scan immediately if possible. The pre-MSAC response reiterated that operator training and experience is important to reduce low quality and invalid scans, and the provided operator training is 3 days. In the real-world setting in Australia, adjusting the operator position, techniques in holding the probe steady were used to reduce these errors of invalid scans or null results. Echolight Italy recommend scanning 10-20 people per new operator. The pre-MSAC response did not identify any particular populations which could result in a greater proportion of lower quality or null or invalid scans and cited conference abstracts that have reported successful REMS in obese patients.

### **Supplementary evidence for test accuracy in different patient groups within the proposed eligible population**

The ADAR included two smaller, single-centre cohort studies, Amorim 2021 and Nowakowska-Plaza 2021, to provide supplementary evidence for the test accuracy of REMS compared to DXA on a greater range of ethnicities and some men.

Amorim 2021 recruited 343 women aged 30-80 years ( $59.9 \pm 10.2$  years) who self-reported their ethnicity as Asian (8.4%), Caucasian (69.6%), African descendent (14.9%) or miscegenated (7.1%). Nowakowska-Plaza 2021 included 116 participants, of which 18 participants were male. After exclusion of scans with quality errors in Amorim 2021, the analysed sample consisted of 66% (227/343 [343 minus 41 DXA - 67 REMS - 10 REMS missing =225]) of lumbar scans and 69% (238/343 [343 minus 30 DXA - 63 REMS=238]) of hip scans. After exclusion of scans with quality errors in Nowakowska-Plaza 2021, the analysed sample consisted of 52% (58/111 [111 minus 40 DXA - 10 REMS - 3 REMS missing]) of lumbar scans and 57% 66/115 [115 minus 36 DXA - 11 REMS - 1 DXA missing - 1 REMS missing]).

Adami 2020 recruited Caucasian women aged 30-90 years. The sample included 1,516 with 1,370 (90%) patients completing the study as 146 patients dropped out due to voluntary drop-out or death.

Given the high number of excluded scans in Amorim 2021 and Nowakowska-Plaza 2021, the risk of bias for flow and timing was considered to be 'unclear'.

**Table 6 Key features of the included evidence**

Criterion	Type of evidence supplied	Extent of evidence supplied	Overall risk of bias in evidence base
Accuracy and performance of the test (cross-sectional accuracy)	Multicentre, cross-sectional, observational cohort, prospective from Cortet 2021 and Di Paola 2019 EchoLight Italy Nov 2017 was a sub study of Di Paola 2019	☒ k=2 n=6,221 (4,307+1,914)	QUADAS-2 checklist Cortet 2021 and Di Paola 2019 low risk with unclear risk for 'Patient selection' and unclear risk of 'Flow and timing'.
Accuracy and performance of the test (cross-sectional accuracy)	Cross-sectional, observational cohort, prospective from Amorim 2021 and Nowakowska-Plaza 2021	☒ k=2 n=459 (343+116)	QUADAS-2 checklist Amorim 2021 and Nowakowska-Plaza 2019 low risk for 'Patient selection' and unclear risk of 'Flow and timing'.
Health outcomes - fracture risk prediction concordance identification	Cross-sectional, observational cohort, prospective, longitudinal from Adami 2020	☒ k=1 n=1,370	Cochrane risk of bias tool Risk of bias: Low Inconsistency: NA Indirectness: NA Imprecision: Low Publication bias: Low (5-year study) Other: NA

Source: Table 46 and Table 47 of the MSAC 1665 ADAR and data from Amorim 2021 and Nowakowska-Plaza 2019.  
k= number of studies, n= number of patients; NA= not applicable; QUADAS-2= Quality Assessment of Diagnostic Accuracy Studies 2.

In order to support the noninferiority claim of REMS compared to DXA in different patient groups within the proposed eligible population (including but not limited to men, obese/large BMI patients, younger populations, different racial populations), the ADAR also relied on preliminary results of studies and their conference abstracts (Ciardo 2021, Cortet 2021 European E-Congress of Rheumatology [EULAR], Cortet 2021 Virtual World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases, Cavalli 2019, Conradie 2014, Tomai 2019, Decianu 2018). An assessment of risk of bias was not conducted for these supplementary studies.

## 11. Comparative safety

No safety data were presented in any of the studies. The ADAR noted that, instead of harms from the scanning process, harms may arise from:

- Incorrect diagnosis with either technology. Given that no major differences were noted between REMS and DXA in terms of providing a wrong diagnosis, no differences are expected in safety between the interventions. The commentary considered it reasonable that there are no specific harms attributed to differences between REMS and DXA regarding potential for wrong diagnosis. Although concordance was not 100%, it is not possible to say whether these differences may result in fewer or more cases of osteoporosis being diagnosed. However, given that no safety data was provided addressing the potential for adverse events, the appropriateness of the safety claim could not be appraised.
- Ionising radiation with DXA in very specific populations (e.g. pregnant women). It is unlikely that a pregnant woman will undergo a DXA. In addition, the low exposure of patients to radiation from a DXA scan should be reiterated. "To compare the 0.5 µSv [microsieverts] received from a lumbar spine DXA scan, the International Atomic Energy Agency (IAEA) reports that the effective dose received from natural background radiation in one day is about 10 µSv." (p.11-12, MSAC 1665 [PICO confirmation](#)). Further, the

ADAR only provided data for the diagnosis of osteoporosis rather than monitoring response to treatment, therefore, the claim that young people may benefit from the avoidance of radiation from the cumulative number of scans may be unsupported. Despite this, the provision of an additional diagnostic modality that avoids any radiation exposure may provide patients with greater consumer choice.

## 12. Comparative effectiveness

### General issues related to the outcomes

1. DXA as the reference standard: PASC “concluded that comparison of BMD measurement with DXA as the reference standard was appropriate but should take into consideration the limitations of DXA.” (p.13, MSAC 1665 [PICO confirmation](#)). This has implications regarding the interpretation of the rate of discordant results between REMS and DXA. Results showing less than 100% for the categorisation of osteoporosis (T-score  $\leq -2.5$ ) or osteopenia ( $-2.5 < \text{T-score} < -1.0$ ) or healthy patients (T-score  $> -1.0$ ) does not necessarily mean that REMS is worse than DXA.
2. Lack of noninferiority margins proposed: The ADAR did not specify any noninferiority margins for the outcomes. However, given that REMS reports on the same parameter (i.e. T-score), reporting on the concordance of REMS and DXA was appropriate to establish noninferiority. If REMS and DXA are concordant, it may be reasonable to infer that there would be no difference in management upon diagnosis of osteoporosis and that health outcomes would be noninferior (p.82 of the [MSAC guidelines](#)). Given that concordance was not 100%, direction of the discordance is unclear in terms of whether it may lead to fewer or more cases of osteoporosis being diagnosed. The results of the key studies Cortet 2021 and Di Paola 2019 from the supplementary ‘unchecked real-world’ analysis showed a poorer correlation and diagnostic concordance in comparison to the primary analysis. However, as no noninferiority margin was defined, the claim of noninferiority may still be met. Similarly, the supplementary study Amorim 2021 demonstrated lower discrimination between patients diagnosed with osteoporosis, osteopenia or healthy compared to the key studies. The pre-ESC response reiterated the claim that REMS and DXA are concordant and so it is reasonable to infer that there would be no difference in management upon diagnosis of osteoporosis and health outcomes would be noninferior.
3. Z-score not reported in the evidence: Z-score based analyses for REMS vs. DXA were not presented in the ADAR. A Z-score is more relevant when there is a potential diagnosis of secondary osteoporosis and is most commonly used in the paediatric population, women who are pre-menopausal and men aged 50 years and under. This patient population may fall under the restriction specified in the MBS items approved for DXA and would have a clinical need for Z-score. The latter suggests that the listing of REMS in patients’ populations where Z score is relevant, may not be supported by the evidence. Only a minority of the patients recruited in the two key studies would have fallen under the category of a patient who would benefit more with a Z-score (i.e. pre-menopausal women). The pre-MSAC response acknowledged that not all relevant populations have been investigated but claimed the evidence does not suggest REMS would be inappropriate for use in these populations. There is emerging evidence on the use of REMS for men, male and female adolescents, young women with anorexia nervosa, pregnant women, differing BMI categories (including overweight and obese) and the use of REMS is increasing in these populations. The pre-MSAC response also highlighted that Z-scores are not referred to in Australian Guidelines, or MBS or PBS criteria.



**Comparison of test accuracy (key studies) – primary quality checked scenario (i.e. excluding REMS and DXA scans with quality errors)**

The results of the comparative analysis of test accuracy for REMS versus DXA (for the lumbar spine and femoral neck sites) for the quality checked scenario (i.e. exclusion of REMS and DXA scans with quality errors) from the key studies (Cortet 2021 and Di Paola 2019) are presented in Table 7. This also includes the additional total femur score results provided by the applicant post-submission of the ADAR.

MSAC did not rely on this scenario when considering the comparative effectiveness of REMS vs DXA as the pre-MSAC response stated that the unchecked/real life scenario is more consistent with clinical practice and that the REMS software can still process and produce results when the scans are considered as “low-quality”. Rather MSAC considered the subsequent supplementary unchecked “real-life” scenario (i.e. only excluding DXA scans with quality errors) the appropriate analysis for comparing the effectiveness of REMS vs DXA.

**Table 7 Quality checked scenario: Key study results (Cortet 2021, Di Paola 2019) and data from Echolight Italy (Nov 2017)**

Outcomes	Cortet 2021		Di Paola 2019		EchoLight Nov 2017
	Lumbar spine	Femoral neck	Lumbar spine	Femoral neck	Total femur
Total scans, N	4,245	1,553	4,271	1,637	1,637
Excluded DXA scans, N (%)	408 (10%)	78 (5%)	340 (8%)	59 (4%)	276 (14%)
Excluded REMS scans, N (%)	373 (9%)	280 (18%)	323 (8%)	205 (13%)	239 (12%)
Retained cases, N (%)	3464 (80%)	1195 (62%)	3608 (84%)	1373 (72%)	1122 (69%)
<b>Correlation/agreement (BMD values)</b>					
Regression line slope	0.90	0.97	0.95	0.97	
Pearson correlation coefficient (r)	0.88 corrected [0.94]	0.93	0.94*	0.93*	-
Coefficient of determination (r <sup>2</sup> )	0.94 corrected [0.88]	0.86	0.89*	0.87*	0.94*
Standard error of estimate (SEE), g/cm <sup>2</sup>	0.042	0.044	0.044 (5.3%)	0.038 (5.8%)	-
<b>Diagnostic accuracy of REMS vs DXA based on with/without osteoporosis categorisation<sup>a</sup></b>					
Sensitivity	90.9%	91.7%	90.4%	91.5%	92.3%
Specificity	95.1%	92.0%	95.5%	91.8%	96.8%
Positive predictive value (PPV)	85.7%	NR	82.3%	NR	-
Negative predictive value (NPV)	97.0%	NR	97.7%	NR	-
<b>T-score based analysis<sup>b</sup></b>					
Diagnostic concordance (with osteoporosis/osteopenic/healthy <sup>a</sup> )	86.8%	86.0%	88.8%	88.2%	84.7%
Cohens k (with osteoporosis/osteopenic/healthy <sup>a</sup> )	0.84	0.83	0.824*	0.794*	-
Median T-score (IQR) with previous osteoporotic fractures:					-
DXA	-2.1 (-2.7, -1.3)	-2.1 (-2.6, -1.4)	NR	NR	-
REMS	-2.3 (-2.8, -1.5)	-2.4 (-2.8, -1.6)	NR	NR	-
Median T-score (IQR) without previous osteoporotic fractures:					-
DXA	-1.6 (-2.4, -0.7)**	-1.6 (-2.3, -0.9)**	NR	NR	-

REMS	-1.7 (-2.4, -0.8)**	-1.6 (-2.4, -0.9)**	NR	NR	-
<b>AUC of T-score ROC curve for discriminating between groups with/without previous osteoporotic fractures<sup>c</sup></b>					
DXA	0.603***	NR	0.631*	NR	-
REMS	0.640***	NR	0.638*	NR	-

Source: Table 6, p38 of the MSAC 1665 ADAR; Additional data from EchoLight Italy, Total Femur, Nov 2017 (unpublished)  
AUC= area under the curve; BMD= bone mineral density; DXA= dual energy x-ray absorptiometry; IQR= interquartile ratio; NR= not reported; REMS= radiofrequency echographic multi spectrometry; ROC= receiver operating characteristic.

Notes:

a. Osteoporosis (T-score  $\leq$ -2.5), Without Osteoporosis includes Osteopenia (T-score -2.5 < to <-1.0), Healthy (T-score >-1.0)

b. The diagnostic concordance was assessed as the percentage of patients classified in the same diagnostic category (osteoporotic, osteopenic, or healthy) by both DXA and REMS and by Cohen's kappa (k).

c. The reference standard for the ROC curve was previous fracture as confirmed by patient clinical history. AUCROC values below 0.7 but more than 0.5 indicate 'low test accuracy'.

\* p<0.001

\*\* p<0.0001 for comparisons with and without osteoporotic fractures

\*\*\* p=0.0002

Table 7 also includes the additional total femur score results from EchoLight Italy provided by the applicant post-submission of the ADAR. This data was provided to address the concerns raised in the PICO confirmation that REMS is not able to provide a BMD measurement for the TPF. Instead, the applicant claimed that the REMS total femur score (a composite of the femoral neck and upper trochanter) can be considered equivalent to the DXA TPF measurement. In the EchoLight Italy report, the correlation of the REMS total femur score and the DXA TPF BMD regression line slope was not reported, but the  $r^2$  was 0.94 (p<0.001), indicating statistically significant high correlation for the REMS total femur score. The diagnostic concordance between the REMS total femur score and the DXA TPF in diagnosing osteoporosis/osteopenia/healthy was 84.7% (with Cohen's K not reported). Overall, the commentary considered the unpublished EchoLight Italy results of the total femur score appear to be consistent with the Di Paola 2019 femoral neck data and appeared to provide support for the use of REMS for proximal femur assuming MSAC consider this evidence demonstrates equivalence to the DXA TPF. However, only a quality checked primary analysis was conducted and hence, the real-world supplementary analysis comparison could not be conducted.

### **Comparison of test accuracy (key studies) – supplementary unchecked “real-life” scenario (i.e. only excluding DXA scans with quality errors)**

Supplementary analyses of both key studies provided results for an expanded analysis that re-included REMS scans with quality errors that were initially removed from the primary dataset. The studies and ADAR stated that this provided a more “real world” population analysis (Table 8). The additional data from EchoLight Italy provided post-ADAR submission did not include a supplementary analysis for the total femur score.

The results of the supplementary dataset were similar across Cortet 2021 and Di Paola 2019 in that correlation, diagnostic concordance of sensitivity and specificity and disease classification were lower compared to the related primary analysis. In Di Paola 2019, when the “supplementary dataset” was considered, the diagnostic concordance was 76.4% (Cohens k = 0.629, p < 0.001) for lumbar spine and 81.9% (Cohens k = 0.691, p < 0.001) for femoral neck.

MSAC noted that the pre-MSAC response stated that the unchecked/real life scenario is more consistent with clinical practice and that the REMS software can still process and produce results when the scans are considered as “low-quality” (that is, the scan was not centralised), but that “invalid” scans (that is, the scan did not lock on to a region of interest) are not reported. Therefore, MSAC considered the unchecked real-life scenario when evaluating the comparative effectiveness of REMS vs DXA.

**Table 8 Key study results: Unchecked 'real-world' scenario results**

Outcomes	Cortet 2021 – Lumbar spine	Di Paola 2019 – Lumbar spine	Cortet 2021 – Femoral neck	Di Paola 2019 – Femoral neck
Enrolled patients, N	4307	1914	4307	1914
Total scans, N	4,245 (99%)	1,553 (81%)	4,271 (99%)	1,637 (86%)
Excluded DXA scans, N (%)	408 (10%)	78 (5%)	340 (8%)	59 (4%)
Excluded REMS scans, N (%)	0	0	0	0
Retained cases, N (%)	3837 (89%)	1475 (77%)	3931 (91%)	1578 (82%)
<b>Correlation/agreement (BMD values)</b>				
Regression line slope	0.82	0.78	0.90	0.86
Pearson correlation coefficient (r)	0.90	0.80*	0.88	0.83*
Coefficient of determination (r <sup>2</sup> )	NR	0.63*	NR	0.70*
Standard error of estimate (SEE), g/cm <sup>2</sup>	0.052	0.085 (10.0%)	0.054	0.064 (9.6%)
<b>Diagnostic accuracy/ of REMS vs DXA based on with/without osteoporosis categorisation<sup>a</sup></b>				
Sensitivity	89.0%	81.0%	85.5%	81.7%
Specificity	94.3%	84.3%	94.5%	89.7%
Positive predictive value (PPV)	NR	NR	NR	NR
Negative predictive value (NPV)	NR	NR	NR	NR
<b>T-score based analysis<sup>b</sup></b>				
Diagnostic concordance (with osteoporosis / osteopenic / healthy <sup>a</sup> )	83.4%	76.4%	82.7%	81.9%
Cohens k (with osteoporosis / osteopenic / healthy <sup>a</sup> )	0.81	0.629*	0.77	0.691*

Source: Adapted from Table 9, p48 of the MSAC 1665 ADAR. Data sources (publications): Cortet 2021 p. 3-6; Di Paola 2019 p. 396-398, Supplementary appendix Table S1

BMD= bone mineral density; DXA= dual energy x-ray absorptiometry; NR= not reported; REMS= radiofrequency echographic multi spectrometry.

a. Osteoporosis (T-score  $\leq -2.5$ ), Without Osteoporosis includes Osteopenia (T-score  $-2.5 < \text{to} < -1.0$ ), Healthy (T-score  $> -1.0$ )

b. The diagnostic concordance was assessed as the percentage of patients classified in the same diagnostic category (osteoporotic, osteopenic, or healthy) by both DXA and REMS and by Cohen's kappa (k).

\*  $p < 0.001$ .

### Comparison of test accuracy (supplementary studies) - use of REMS for patient groups within the proposed eligible population

The ADAR presented data from Amorim 2021 and Nowakowska-Plaza 2021 as supplementary evidence for test accuracy of REMS compared to DXA in a greater range of ethnicities and some men (Table 9). Amorim 2021 recruited 343 women aged 30-80 years ( $59.9 \pm 10.2$  years) and included women who self-reported their ethnicity as Asian (8.4%), Caucasian (69.6%), African descendent (14.9%) or miscegenated (7.1%). Nowakowska-Plaza 2021 included 116 participants aged 40-87 years, of which 18 participants were male. The diagnostic concordance in Amorim 2021 was lower than the key studies with 67.1% (Cohens k =0.47) and 71.4% (Cohens k =0.53) for lumbar spine and femoral neck, respectively. The authors noted that non-concordant diagnoses were concentrated on those DXA classified as normal and REMS classified as osteopenia. The correlation of BMD scores was high and statistically significant for both Amorim 2021 and Nowakowska-Plaza 2021. The sensitivity and specificity for the subgroup of over 40 years in Amorin 2021 was high (not reported in Nowakowska-Plaza 2021).

**Table 9 Supplementary test accuracy results (Amorim 2021, Nowakowska-Plaza 2021)**

Outcomes	Amorim 2021		Nowakowska-Plaza 2021	
	Lumbar spine	Femoral neck	Lumbar spine	Femoral neck
Total scans, N	333	331	115	111
Retained cases, N	227	238	66	58
Female, n (%)	343 (100%)		53 (91.4%)	53 (80.3%)
Caucasian, n (%)	224 (69.6%)		116 (100%)	
<b>Correlation/agreement (BMD analysis)</b>				
Regression line slope	-	-	-	-
Pearson correlation coefficient (r)	0.75*	0.78*	-	-
Spearman's coefficient	-	-	0.839*	0.867*
Coefficient of determination (r <sup>2</sup> )	-	-	-	-
Standard error of estimate (SEE), g/cm <sup>2</sup>	-	-	-	-
<b>Diagnostic accuracy of REMS vs DXA based on with/without osteoporosis categorisation<sup>a</sup></b>	<b>(&gt;40 years)</b>	<b>(&gt;40 years)</b>		
Sensitivity	80%	85%	-	-
Specificity	94%	93%	-	-
Positive predictive value (PPV)	-	-	-	-
Negative predictive value (NPV)	-	-	-	-
<b>T-score based analysis<sup>b</sup></b>				
Diagnostic accuracy (with osteoporosis / osteopenic / healthy <sup>a</sup> )	67.1%	71.4%	82.8%	84.8%
Cohens k (with osteoporosis / osteopenic / healthy <sup>a</sup> )	0.47	0.53	0.611	0.667

Source: Table 16, MSAC 1665 ADAR

\* p<0.001

Notes:

a. Osteoporosis (T-score ≤-2.5), Without Osteoporosis includes Osteopenia (T-score -2.5 < to <-1.0), Healthy (T-score >-1.0)

b. The diagnostic concordance was assessed as the percentage of patients classified in the same diagnostic category (osteoporotic, osteopenic, or healthy) by both DXA and REMS and by the Cohen's kappa (k).

## Predicting incident fragility fractures

A longitudinal study by Adami 2020 with a mean follow-up of 3.7 ± 0.8 years (median ± interquartile range: 3.5 ± 1.7 years; range: 1.9–5.0 years), showed that the incidence of clinical fragility fractures was 14.0%. It was not reported if Adami 2020 was powered to detect a difference in fracture rate at the follow-up time point.

REMS and DXA reported statistically significant odds ratios (OR) for lumbar spine DXA (1.7, p=0.0032) and REMS (2.6, p<0.001); and femoral neck DXA (2.68, p<0.001) and REMS (2.81, p<0.001) (Table 10). The results from this study should be interpreted with caution given the sensitivity was low for REMS (65.1% lumbar spine and 40.2% femoral neck) and DXA (57.1% lumbar spine and 42.3% femoral neck). Although REMS may provide consistent BMD scores to the gold standard DXA, the use of BMD (measured by DXA or REMS) may not be sufficient to predict fracture risk. Therefore, the commentary considered the reliance of a longitudinal accuracy study to support the claim of BMD test and longer-term fracture risk should be interpreted with caution.

**Table 10 Predicting incident fragility fractures based on osteoporotic/non-osteoporotic classification (Adami 2020)**

Outcome		Lumbar spine / vertebral		Femoral neck	
<b>Osteoporotic and non-osteoporotic patients<sup>+</sup>: identification of incident fragility fracture*</b>					
DXA	Sensitivity	57.1%	<b>OR 1.7; p=0.0032 (95% CI 1.20, 2.51)</b>	42.3%	<b>OR 2.68; p&lt;0.001 (95% CI 1.71, 4.21)</b>
	Specificity	56.3%		79.3%	
REMS	Sensitivity	65.1%	<b>OR 2.6; p&lt;0.000 (95% CI 1.77, 3.76)</b>	40.2%	<b>OR 2.81; p&lt;0.001 (95% CI 1.80, 4.39)</b>
	Specificity	57.7%		79.9%	
<b>Identified as “healthy” who did not have a fracture during follow-up</b>					
DXA	% patients	75.6%	-	NR	-
REMS	% patients	74.5%	-	NR	-
<b>Identified as “osteoporotic” who had a fracture during follow-up</b>					
DXA	% patients	39.5%		NR	
REMS	% patients	43.7%		NR	
<b>Identified as “osteopenic” who had a fracture during follow-up</b>					
DXA	% patients	29.1%	-	NR	-
REMS	% patients	21.9%	-	NR	-

Source: Table 14, MSAC 1665 ADAR

CI= confidence intervals; DXA= dual energy x-ray absorptiometry; NR= not reported; OR= odds ratio; REMS= radiofrequency echographic multi spectrometry.

+ Osteoporosis (T-score  $\leq$ -2.5), Without Osteoporosis includes Osteopenia (T-score -2.5 < to <-1.0), Healthy (T-score >-1.0)

\* Reference standard is identification of incident fragility fracture (medical imaging investigations) over the follow-up period.

In the age-matched/adjusted and BMI-adjusted comparisons of the sensitivity/specificity of REMS and DXA to discriminate between groups that subsequently developed or did not develop fractures, REMS had statistically significantly better discriminatory ability based on the lumbar spine T-score, compared with DXA ( $p \leq 0.001$ ) (Table 11). The ROC curves of sensitivity vs. 1 minus specificity (i.e. AUC of both REMS and DXA >0.5, signifies discriminatory ability for lumbar spine). The majority of the AUC reported in Table 11 was below 0.7, indicating a low-test accuracy, with the exception of BMI adjusted REMS for lumbar spine (0.723). There were no statistically significant differences with the femoral neck by fracture sites for REMS compared to DXA.

**Table 11 AUC for lumbar spine and femoral neck DXA and REMS T-score values by all and specific fracture sites (Adami 2020)**

Dataset (overall)	Fracture site	AUC for lumbar spine/vertebral T-score			AUC for femoral neck T-score		
		DXA	REMS	p-value	DXA	REMS	p-value
Age-matched	All sites	0.614	0.657	<b>0.0002</b>	0.65	0.64	0.38
Age-adjusted	All sites	0.597	0.631	<b>0.001</b>	0.583	0.627	0.06
BMI-adjusted	All sites	0.692	0.723	<b>0.001</b>	0.674	0.695	0.24
Age and BMI-adjusted	All sites	0.613	0.649	<b>0.001</b>	0.596	0.632	0.08
	Vertebra	0.78	0.781	0.99	0.590	0.622	0.60
	Hip	0.674	0.664	0.67	0.616	0.602	0.78
	Other sites	0.545	0.594	<b>0.001</b>	0.567	0.611	0.07

Source: Adami 2021 p. 5-6, Table 2

AUC= area under the curve; BMI= body mass index; DXA= dual energy x-ray absorptiometry; REMS= radiofrequency echographic multi spectrometry.

P-values are from Delong test of equivalence between ROC curves.

The reference standard was incident fragility fractures confirmed by imaging investigations.

The MSAC Guidelines state that for values above 0.9, test accuracy was high; for values between 0.7 and 0.9, test accuracy is moderate; and for values below 0.7, test accuracy low. An area under the receiver operating characteristic (AUROC) value of  $\leq 0.50$  indicates that the test cannot discriminate between true positives and true negatives, with the curve lying on or below the major diagonal” (p.277 MSAC Guidelines, Version 16. Final).

### Supplementary data for other patient groups within the proposed eligible population

Overall, the additional evidence for other patient groups within the proposed eligible population was supportive, but not conclusive, of the use of REMS in comparison to DXA. There are important limitations from the evidence, mainly regarding incomplete reporting in conference abstracts and overall paucity of data.

### Clinical claim

The ADAR claimed that the use of REMS for BMD measurement for diagnosis of osteoporosis resulted in noninferior effectiveness compared with DXA. Overall, the commentary considered that the claim on noninferiority of effectiveness was supported by the data for BMD and T-score at lumbar spine, femoral neck and total femur (although no real-world scenario reported) sites for post-menopausal women based on the two key studies. However, there is a paucity of data in certain populations including males, younger women, children and different ethnicities from Caucasian. These patient populations would require a Z-score analysis which was not provided in the ADAR.

The key clinical studies highlight that the rate of REMS scans with quality errors is operator-dependent, which has implications for the number of repeat scans. This highlights the need for a rigorous training and possible ongoing quality checks for REMS. Further, the ADAR did not specifically report the rate of unsuccessful (invalid) scans (failure to complete the scan despite reattempts) or the rate of repeat/alternative (DXA or qCT<sup>21</sup>) scans as a result of unsuccessful REMS scans as specified in the [PICO confirmation](#).

The ADAR claimed that the use of REMS results in noninferior safety compared with DXA. The commentary considered it reasonable that there are no specific harms attributed to differences between REMS and DXA regarding potential for wrong diagnosis.

<sup>21</sup> quantitative computed tomography

### 13. Economic evaluation

The ADAR intended to present a cost-minimisation analysis (CMA) based on the clinical claim of noninferior safety and effectiveness of REMS compared to DXA; this intention was considered appropriate. The commentary noted that the ADAR however appeared to have presented a fee justification rather than a CMA of the total comparative costs for REMS versus DXA.

Table 12 shows the disaggregated costs to perform and deliver a bone densitometry scan using REMS which includes costs for the device, operator wages, clinical space and physician review.

The time required to provide the service is based on the Cortex Health experience across several instances including:

1. providing REMS training to clinicians
2. invitation to a GP clinic to scan several patients
3. REMS patient Clinics in Westmead hospital
4. data provided by Echolight Italy where the service is now routinely provided.

**Table 12 Disaggregated costs for the delivery of REMS (per service)**

Parameter	Time (minutes)	Value	Description or source
<b>Capital costs</b>			
Device cost		\$24.00	EchoStation cost (\$72,000) after 3,000 tests
<b>Service delivery costs</b>			
Patient commencement & data entry, positioning & gel application	6	\$30.00	\$60/hour assumed equivalent to nurse award
Left femoral neck scan	5		Probe placement, adjustments, scan and analysis
Right femoral neck scan	5		Probe placement, adjustments, scan and analysis
L1-L4 lumbar spine	8		Probe placement, adjustments, scan and analysis
Final check, reports saved, emailed & prepare for next patient	6		
Access to private room & examination bench		\$33.33	Clinic room hire (\$500/day)
Physician review of report	10	\$33.33	\$200/hour assumed
Ultrasound gel		\$3.00	\$100/5 litres. Use approximately 50ml/site
<b>Total (including device cost)</b>	<b>30</b>	<b>\$123.67</b>	
<b>Total (excluding device cost)</b>		<b>\$99.66</b>	

Source: Table 21, p70 of the MSAC 1665 ADAR

HCP= health care provider; REMS= radiofrequency echographic multi spectrometry.

Including capital device costs, the ADAR estimated the direct cost of REMS per patient as \$123.67. REMS was assumed to replace DXA assuming a 1:1 substitution on a per patient basis and no other additional costs or cost-offsets were identified. The ADAR compared the cost of REMS against the cost (MBS schedule fee) of DXA of \$106.55. On this basis, the net difference between REMS and DXA is \$17.12 (\$123.67-\$106.55).

Excluding capital device costs, the estimated direct cost of REMS per patient was \$99.66. This was less than the proposed MBS fee for REMS and the existing MBS fee for DXA of \$106.55. However, the ADAR may have underestimated the service delivery costs for REMS as the times proposed are estimates from the applicant without supporting sources and the applicant acknowledges uncertainties around the time estimates. It is unknown whether or not studies reported times for scans and that the time to deliver the REMS service may be increased if

difficulties are encountered locating the region of interest for the scan. Therefore, the commentary considered that the time it takes to conduct a scan is likely more than it takes to conduct a DXA, particularly as there may be a higher failure rate of ultrasound scans at one or more skeletal sites, which may reduce patient utilisation (as noted in the consultation responses).

The ADAR estimated the time to conduct the REMS scan including patient commencement, three skeletal site scans and final check would take 30 minutes. No additional data was provided for length of consultation if a repeat scan was necessary for one of the skeletal sites. If either a left or right femoral neck scan was unsuccessful, a repeat scan would take an additional 5 minutes. Similarly, if a L1-L4 lumbar spine scan was unsuccessful, an additional 8 minutes would be required. This would have implications for the staffing cost of delivering the scan as well as the clinic room hire.

The pre-MSAC response stated that the time allocation was based on experience at Australian sites and considered the 30 minutes proposed to be an overestimate suggesting this time would allow for a non-rushed experience with the operator and patient. The pre-MSAC response also highlighted that DXA scans may include partial undressing (if any metal on clothing), positioning and strapping of leg stabilisers, using the motorised overhead, scanning, data entry and waiting for results at each site and countered that the DXA scans of all 3 sites would take at least the same amount of time as for REMS.

The ADAR did not address issues regarding problems with scans that may result in additional BMD testing:

- The need for a repeat scan if the initial REMS scan was considered invalid or low-quality.
- The potential for additional DXAs for patients who may receive both scans in a situation where the initial REMS scan was unsuccessful (the rate of unsuccessful scans was not addressed in the ADAR). The pre-MSAC response noted that patients can be re-scanned immediately if they receive an invalid or null result and estimated that <5% of patients would end up needing a DXA or qCT scan claiming this would only be needed in the case of severe and unexpected osteoporosis.

If the ADAR's intention was to consider and present the total comparative costs for REMS versus DXA, the commentary noted that the ADAR may have underestimated the total costs of REMS. It was acknowledged that the MBS fee would be fixed, hence, if there are increased costs of the device including capital, transport or training, then this would not result in any net change in expenditure to the MBS. The underestimation of the costs of REMS (beyond the MBS) may be due to the following:

- The cost of transporting the device to each patient was not included. This could be via wheeling the REMS device into an inpatient setting, a residential aged care facility or a rural/remote setting. The pre-ESC response noted that once the REMS device is set up, it would likely remain within a treatment room. The portability allows it to be moved from clinic to clinic in preparation for outpatient settings or to the patient (if the patient is immobile); this would not increase the cost of assessments.
- The cost of training to use the REMS device was not included. The latter may also include an ongoing quality check. The key studies highlighted the importance of training given the rate of REMS scans with quality errors. The pre-MSAC response stated that a 3-day training package is included in the cost of the device per clinic and 6-monthly quality checks (including refresher training and software updates) at an estimated \$1,000 to \$2,000 per quality check.
- The ADAR estimated the cost of the device assuming 20 scans per week over 3 years (3,000 [20 tests/week \* 52 weeks/year \* 3 years = 3,120]); however, this was not



referenced nor supported by any data. If the device is underutilised and less than 20 scans are conducted per week, then the overall cost of the device will likely be higher.

- The device cost corresponded to the EchoStation. The ADAR did not justify why the EchoStation device was relied on in the cost-minimisation compared to the other three devices. In particular, EchoStation is the cheapest device and the only device that is not portable, a characteristic that the ADAR had presented as an advantage to DXA as it would allow facilitated access to regional and remote communities, Aboriginal and Torres Strait Islander populations and communities, elderly and frail who have reduced mobility, those with bone deformity / difficulty who cannot lie perfectly supine, patients with surgical intervention such as hip fracture surgery using rods and nails (p. 5 and 10, MSAC 1665 PICO Confirmation). It may have been more appropriate to use the device cost of the EchoHybrid which is a portable version of the device equating to \$89,375 including GST. Using the EchoHybrid device cost, which was estimated to be \$28.65 ( $\$89,375 / (20 \text{ tests/week} * 52 \text{ weeks/year} * 3 \text{ years})$ ), the net difference between the REMS and DXA based increases to \$21.76 ( $\$128.31 - \$106.55$ ). The pre-ESC response indicated that the EchoStation was chosen as this model, while not fully portable, is the most appropriate clinical device when comparing to a fixed DXA unit. It further indicated that the base model (the EchoS) is approximately \$8,000 cheaper than the EchoStation, is fully portable to measure BMD, but is slower and unable to take on additional functionality due to computer/laptop limitations.

## 14. Financial/budgetary impacts

The ADAR followed a market share approach to estimate the financial implications of the proposed MBS listing of REMS based on the current MBS utilisation of DXA, assuming replacement of some DXA scans by REMS across the analogous MBS items. The financial implications to the MBS resulting from the proposed listing of REMS are summarised in Table 13. The financial implications are presented over 6 years.

**Table 13 Net financial implications of REMS to the MBS**

Parameter	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Total estimated use of DXA or REMS bone densitometry services</b>						
Number of services	605,080	605,080	605,080	605,080	605,080	605,080
<b>Estimated use and cost of the proposed health technology (REMS) – substitution of DXA only</b>						
Estimated uptake of REMS	5%	7%	10%	12%	13%	15%
Number of services of REMS	30,254	42,356	60,508	72,610	78,660	90,762
Cost to the MBS	\$2,741,012	\$3,837,417	\$5,482,025	\$6,578,430	\$7,126,632	\$8,223,037
<b>Change in use and cost of other health technologies (DXA)</b>						
Change in use of DXA	-30,254	-42,356	-60,508	-72,610	-78,660	-90,762
Net change in costs to the MBS	-\$2,741,012	-\$3,837,417	-\$5,482,025	-\$6,578,430	-\$7,126,632	-\$8,223,037
<b>Net financial impact to the MBS</b>	<b>\$0</b>	<b>\$0</b>	<b>\$0</b>	<b>\$0</b>	<b>\$0</b>	<b>\$0</b>
<b>Additional ADAR scenario – Market growth assuming additional 7.5% in services of REMS</b>						
Additional services (number of REMS services x 7.5%)	2,269	3,177	4,538	5,446	5,900	6,807
<b>Net financial impact to the MBS -additional 7.5% in REMS services</b>	<b>\$205,576</b>	<b>\$287,806</b>	<b>\$411,152</b>	<b>\$493,382</b>	<b>\$534,497</b>	<b>\$616,728</b>
Then the increase (%) of total spend equates to*	0.37%	0.52%	0.75%	0.90%	0.97%	1.13%

Source: Table 31 of the MSAC 1665 ADAR with commentary in italics

DXA= dual energy x-ray absorptiometry; MBS= Medicare Benefit Schedule; REMS = radiofrequency echographic multi spectrometry  
 Cost per service (85% benefit level, \$90.60)

\* If total MBS spend on DXA & REMS: \$54,820,248 (605,080 MBS services for 2021 multiplied by \$90.60)

\*\* The net financial impact to the MBS under a 7.5% increase in REMS divided by the total spend on MBS and PBS from REMS or DXA in the base case

Key assumptions in the analysis were:

- Maximum of one service per patient per year (given restrictions on repeat services of minimum 1-5 years), hence patient and service numbers was identical. This seemed reasonable.
- No growth in the DXA usage (in the absence of REMS) was predicted, based on MBS services data over the last 3 years (no growth, on average). It may not have been appropriate to only review data over the last 3 years (2019-2021) to inform the assumption of no growth. The variability in the number of services provided across 2019 to 2021 will likely have been affected by the COVID-19 pandemic. The assumption of no growth was not supported based on 4 years of utilisation data which demonstrated that, on average, there has been a 5% increase in utilisation per year since January 2018 to December 2021 (MBS items 12320 and 12322 were listed on 1 November 2017)<sup>22</sup>.
- MBS 85% fee benefit level assumed for REMS and DXA. The MBS benefit fee would equate to \$90.57 (85%\* \$106.55).

<sup>22</sup> Medicare Item Reports, [http://medicarestatistics.humanservices.gov.au/statistics/mbs\\_item.jsp](http://medicarestatistics.humanservices.gov.au/statistics/mbs_item.jsp)

- There were no other MBS cost offsets assumed. The commentary noted that this was reasonable.
- No financial impact on other health budgets was assumed. This was reasonable, noting that more cases could be identified if REMS is to be accessed by patients for which DXA was not suitable/not accessible and would require PBS treatments.
- The ADAR assumed an uptake of 5% of current DXA scans in year 1, increasing gradually to 15% by year 6. The estimation of uptake was not justified in the ADAR nor supported by any data, although possibly low due to potential limited number of devices currently available in Australia. The uptake rate was assumed the same for all MBS items sought, which may not be reasonable.

Overall, the base case (1:1 substitution of DXA with REMS) showed a zero net financial impact. The ADAR additional market growth scenario results suggested that the impact on the MBS, would be minimal, increasing the total MBS spend by 0.37% in Year 1 to 1.13% in Year 6. This scenario assumed a 7.5% increase in the total REMS scan (not a 7.5% growth of the total BMD scan market so only equated to a 0.37%-1.13% increase in total BMD scans) and this assumption was not supported by any data.

The potential financial impact of an increase in total DXA and REMS tests due to use by new patient populations (residential aged care facility, rural and remote setting) who could not access DXA or for whom DXA was not suitable was assumed as a 7.5% increase in the total REMS tests. The estimated financial cost over 6 years would be minimal, equating to a maximum 1.6% of total MBS spend on REMS/DXA by year 6. The use of 7.5% to quantify the potential increase service utilisation due to the availability of REMS was not supported by any data. However, it is possible that the potential increased mobility of the REMS service may increase service utilisation. The commentary noted that “PASC noted that while DXA is not portable, it is currently delivered in rural and remote areas, including via mobile units” p.12, MSAC 1665 [PICO confirmation](#). The overall impact on the governments’ health budget would be higher if:

- There is a larger than 7.5% increase in REMS services due to unmet need from patients with metal prostheses, residential aged care facilities and rural/remote communities.
- Having an additional BMD testing modality available on the MBS increases the rate of BMD testing considering the current underdiagnosis of osteoporosis as stated in the [‘National Strategic Action Plan for Osteoporosis 2019’](#).

The pre-MSAC response acknowledged the 7.5% estimate is subjective but stated that these are small patient populations who at a high need but unable to access DXA testing and so REMS may be clinically important for these patients, however the growth in usage of a new technology will likely take time.

Co-payments were not estimated in the ADAR. The ADAR assumed that some patients who undergo DXA scans face ‘out of pocket’ costs and it was possible that some providers may also apply an ‘out of pocket’ cost to REMS services. The ADAR assumed that there was no reason to expect that this would be higher for REMS than DXA.

Although, REMS is meant to be an alternative to DXA, it is possible that some patients may receive both, a REMS and DXA scan; however, only one item may be claimed within the restricted time period. The ADAR stated that the greater portability of REMS compared with DXA also means that utilisation in rural and remote settings (e.g. remote indigenous communities) may occur. REMS may also be suitable for people who, because of disability or physical limitations, cannot undertake a DXA scan, but are suitable for REMS. While these factors may increase the population in whom it could be used, it is not expected to result in a substantial increase. The ADAR considered that it was appropriate to not consider this as leakage, the commentary noted

that this would have implications on utilisation as the size of the eligible population would increase.

Overall, the financial impact may be underestimated due to:

- The use by new patient populations who could not access DXA including patients living in rural/remote areas, patients with mobility issues living in aged care facilities, and metal prostheses.
- Only considering a 1:1 substitution of REMS/DXA. The cost neutral approach does not consider the possibility of repeat testing with DXA or vice versa. The commentary noted that these will likely represent exceptions as it is anticipated that REMS and DXA services will include appropriate claiming restrictions.
- The assumption of no market growth based on 3-years of utilisation data for DXA MBS items. Given that market growth was observed in the last 4 years for the MBS items, the assumption of no additional market growth may represent an underestimation of utilisation. Under a scenario that the listing of REMS grows the market and is not a complete 1:1 substitution with DXA, then this will have implications for the MBS budget.

## 15. Other relevant information

### Responses to PICO comments about REMS operator training

The applicant advised it is open to dialogue with the relevant professional societies to develop and have accredited a training platform for REMS technology. The ADAR stated that at this stage, it is unclear as to which of these professional bodies are best to initiate discussions with as there is the potential for various specialities to utilise REMS technology. Certainly, the training platform for specialists (endocrinology) will be different to that structured for general practice or regional/remote medical services. Indeed, having a single training platform comprised of various modules could easily be tailored across these different disciplines depending on their base knowledge of bone architecture, osteoporosis, fracture risk, ultrasound etc.

The ADAR indicated that the applicant had not commenced these activities and noted that post submission discussions with these groups would begin with progress updates provided to MSAC.

There are a number of issues remaining regarding the REMS operator training:

- The lack of clarity around the health care professionals that will be conducting the REMS has implications for use of the REMS device and subsequent claiming of the MBS item. This is likely related to the lack of support from professional societies during the consultation feedback.
- In terms of cost of training it is not clear who will pay for the training as it was not included in the cost-minimisation analysis. It may be reasonable to include the cost of the training in the cost of the medical device purchase. Further, the cost of possible ongoing quality checks on training were not discussed in the ADAR.
- It is not possible to comment on the comprehensiveness of the proposed 3-day training program without endorsement advice by any professional society. Importantly, the clinical evidence presented in the ADAR highlights the operator-dependency of the REMS technology and there were varied exclusions of REMS scans dependent on the amount of training provided.

The pre-MSAC response again indicated the applicant would work with any of the Societies who are keen to develop appropriate training programs but did not state whether progress had been made to do so.

## 16. Key issues from ESC to MSAC

### Main issues for MSAC consideration

#### Clinical issues:

- The two key studies comparing the analytical performance of REMS and DXA presented two scenario analyses:
  - Quality checked scenario (“primary analysis”) – where both REMS and DXA scans with identified quality errors were excluded.
  - Unchecked / real-life scenario (“supplementary analysis”) – where REMS scans with quality errors were not excluded while DXA scans with quality errors were excluded.

Until it can be confirmed how REMS scans with quality errors can be identified in practice, it may be preferable for MSAC to rely on the unchecked / real life scenario in the clinical and economic evaluations.

- Across the proposed eligible population (the majority being post-menopausal females), findings from the two studies support a conclusion that REMS has noninferior analytical performance (and thus noninferior effectiveness and noninferior safety) compared to DXA if REMS scans with quality errors are excluded from the analysis (the quality checked scenario).
  - If REMS scans with quality errors would not be identified in Australian practice, then the diagnostic accuracy and correlation reported in the quality checked scenario will not be a reliable representation of REMS performance in practice. Rather the lower diagnostic accuracy and correlation presented in the unchecked real-life scenario analysis would be more applicable.
  - The applicant is requested to respond to the questions presented in Section 8 seeking clarification on whether REMS scans with quality errors would be identified in practice and if so to clearly detail the process for identifying these quality errors.
- In terms of rendering the service, REMS appears to have noninferior safety compared to DXA.
- There is sparse or no direct evidence regarding the performance of REMS in several patient groups that fall within the proposed eligible population, including obese patients, males, younger populations (using a Z-score analysis) and different racial populations. Because of these limits within the evidence base the generalisability of the evidence to patient groups other than post-menopausal females is uncertain.
- It is noted that training and qualification for REMS need to be defined in consultation with relevant professional Australian bodies, and relevant professional societies need to endorse the accredited training program for REMS before implementing any REMS MBS items.

#### Economic issues:

- The appropriateness of a cost-minimisation approach for the economic analysis on a per scan basis is contingent on MSAC accepting the claim of clinical noninferiority, in which case there would be no expectation of a substantial difference in the provision and cost of subsequent healthcare resources.
- There is uncertainty regarding the justification of the MBS fee proposed for REMS. While the estimated per service delivery costs for REMS (excluding capital device costs) (\$99.66) is similar to the MBS fee for a DXA service (\$106.00), it is possible the per service delivery costs for REMS may be higher than estimated by the applicant, and that any amount greater than the proposed cost-minimised fee for REMS of \$106 could be passed on to patients.

**Financial issues:**

- Although the net MBS budget impact is claimed to be nil, there is uncertainty regarding the extent to which REMS will replace DXA, and the extent to which REMS may increase the overall use of imaging for BMD by providing access to eligible patients who, for a range of reasons, currently do not access DXA. Uptake data from other markets was not provided by the applicant.

**ESC discussion**

ESC noted that this application is requesting Medicare Benefits Schedule (MBS) listing of non-invasive ultrasound radiofrequency echographic multi spectrometry (REMS) for the diagnosis of osteoporosis. ESC noted that listing is requested on the basis of a claim of noninferiority (and thus cost minimisation of MBS fees) versus dual-energy x-ray absorptiometry (DXA) as the main and only comparator. REMS is proposed as an alternative to DXA, but would be listed in the General Medical Services Table rather than the Diagnostic Imaging Services Table in the MBS.

ESC noted that the REMS technology was included on the Australian Register of Therapeutic Goods (ARTG) for use in Australia on 28 September 2020. ESC noted that this application is for one brand, Echolight. Through its software, Echolight provides all the standard parameters for the diagnosis of osteoporosis, including bone mineral density (BMD), T-score and Z-score.

ESC noted that public consultation feedback was generally not supportive of the application. Most responses noted that the portability of the REMS device would allow easier access to BMD scans, such as for patients in nursing homes or in rural and remote communities. The feedback also noted that REMS is radiation-free, but ESC noted that the levels of radiation associated with a DXA scan are low (much lower than background radiation). Other benefits noted were that REMS could offer greater flexibility for patients who cannot lie completely supine. However, the feedback also raised several concerns, including the high rate of unsuccessful scans, the limited data for all patient groups within the proposed eligible population, and the inability to retrospectively review scans. Additionally, REMS cannot scan some areas of the body that are measured for certain diseases specified for DXA in the MBS, such as the forearm in patients with hyperparathyroidism. Feedback also noted the need for trained operators, and that higher operation costs may lead to overservicing. ESC noted the lack of consultation feedback from consumers. ESC questioned the proposed advantage of the mobility of the service. ESC requested clarification on the patient groups who currently do not have access to DXA, and whether people living in rural or remote areas, or Aboriginal and Torres Strait Islander people are currently underserved. ESC noted that there are currently only four sites in Australia that have REMS devices, which may initially limit access to REMS, but this number could change rapidly with the resulting ease of access potentially leading to overservicing.

ESC noted that the proposed population for REMS is patients who require BMD measurement for the diagnosis or monitoring of osteoporosis and who are currently eligible for an MBS-funded DXA. ESC noted that patients would be investigated, managed and referred in the same way as for DXA scanning, and the clinical management algorithm for DXA is already well established in Australia by the Royal Australian College of General Practitioners (RACGP). However, ESC was unsure whether patients who are unable to have DXA should be referred to REMS instead of being referred for a quantitative computed tomography (qCT) scan.

ESC noted that the applicant proposed REMS be added to six existing MBS items for DXA (items 12306, 12312, 12315, 12320, 12321 and 12322), with the same fee (\$106.55). However, if MBS funding is supported, PASC and the Department proposed a separate set of items for REMS. ESC considered that a separate set of items would be appropriate as it allows for: a different MBS fee, different Explanatory Notes, different eligible population(s), different limits on scan frequency (if required), tracking of REMS utilisation separate to DXA utilisation, and restrictions on co-claiming of REMS and DXA. However, ESC considered that several factors

required clarification. ESC acknowledged that the pre-ESC response addressed several training/accreditation queries. However, ESC considered that there is a lack of clarity about who would be performing the service. ESC noted that it was the Department's preference that, similar to DXA services, this would be restricted to appropriately qualified providers such as a specialist or consultant physician, or radiographers or sonographers who perform the service under the supervision of a specialist or consultant physician, and the specialist or consultant physician who is responsible for the service performs the interpretation and reporting for the service. ESC also questioned what quality assurance there will be for the operator's qualifications for the use of REMS. ESC considered that training and qualification needs to be defined in consultation with relevant professional Australian bodies, and that relevant professional societies need to endorse the accredited training program for REMS before implementing any REMS MBS items.

ESC also requested clarification on whether the REMS scan can produce a report that allows for the clinician (specialist or consultant physician) who is evaluating the results and providing a report to the referrer to have a clear understanding of whether the scans have been analysed correctly, the details of the associated population reference data being used, and appropriate interventions in response to diagnostic and non-diagnostic results.

Regarding comparative safety, ESC noted that the studies attributed no specific harms to the REMS or DXA scanning process. ESC noted that harms may arise from incorrect diagnosis with either technology, or with DXA from ionising radiation in very specific populations (for example, pregnant women). However, only a very low dose of ionising radiation is required for DXA scans, and women are highly unlikely to undergo DXA whilst pregnant, so ESC considered that this was not a significant concern. ESC considered the claim of noninferior safety of providing REMS compared to DXA to be reasonable.

ESC noted that the evidence base consisted of two cross-sectional studies comparing REMS with DXA (Cortet 2021<sup>23</sup> and Di Paola 2019<sup>24</sup>), and three additional studies as supplementary evidence. The studies were reported to have an overall low risk of bias. However, ESC noted that there was an unclear risk of bias in patient selection for all studies. ESC considered the two cross-sectional studies to be the most informative, as they had the highest patient numbers and were the most applicable to the Australian setting.

ESC noted that quality errors are possible for both DXA and REMS scans and that the studies excluded DXA and REMS scans with quality errors from the primary analysis referred to as the quality checked scenario. ESC also noted that whilst DXA scans can be reanalysed, reducing the number of DXA scans excluded due to quality errors, REMS scans cannot be reanalysed.

Regarding comparative analytical performance (and thus effectiveness and safety based on scan results), ESC noted the studies reported high diagnostic accuracy (sensitivity 90.9%-92.3%; specificity 91.8%-96.8%) of REMS versus DXA in the primary analysis after excluding all scans with quality errors. ESC also noted that diagnostic concordance between REMS and DXA is not 100%, but the direction of the discordance is not known. ESC considered that, across the eligible population (the majority being post-menopausal females), the studies suggest that REMS has noninferior effectiveness compared to DXA after excluding REMS scans with quality errors. However, ESC questioned whether REMS scans with quality errors would be identified in Australian practice and if not, then the diagnostic accuracy and correlation reported for REMS with DXA may not be a reliable representation of REMS performance in practice. Rather the lower diagnostic accuracy and correlation presented in the unchecked real-life scenario (supplementary analysis) would be more representative. Therefore, ESC requested the applicant

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<sup>23</sup> Cortet BE, Dennison E, Diez-Perez A et al. (2021). Radiofrequency echographic multi spectrometry (REMS) for the diagnosis of osteoporosis in a European multicenter clinical context. *Bone* **143**:115786.

<sup>24</sup> Di Paola M, Gatti D, Viapiana O et al. (2019). Radiofrequency echographic multispectrometry compared with dual X-ray absorptiometry for osteoporosis diagnosis on lumbar spine and femoral neck. *Osteoporosis International* **30**(2):391-402.

to respond to the questions presented in Section 8 from the commentary seeking clarification on whether REMS scans with quality errors be identified in practice and if so to provide clarification on the process for identifying quality errors.

ESC also noted that the published studies only focused on the lumbar spine and femoral neck; the total proximal femur (TPF) was not included. ESC noted that the applicant provided unpublished data comparing the REMS total femur score (a composite of the femoral neck and upper trochanter) with the DXA TPF, which showed a high correlation ( $r = 0.94$ ). However, ESC did not consider this comparison to be conclusive, noting that the quality checked primary analysis was not supplemented by an unchecked 'real life' supplementary analysis.

ESC noted that the Z-score was not reported in the evidence, nor was the fragility score. ESC noted that there was a sparsity or lack of evidence supporting the use of REMS in several patient groups that would be within scope for the proposed MBS listing, including: obese patients; males; younger populations and different racial populations. ESC also noted that REMS can only scan the lumbar spine and femur, therefore REMS would not be used in populations that required a BMD measurement at another site (e.g., distal forearm scan for patients with hyperparathyroidism). Although ESC noted the sparsity or lack of direct comparative evidence created some uncertainty in the claim that REMS has noninferior effectiveness compared to DXA for all patient groups within the proposed eligible population, ESC questioned whether restricting REMS would create equity issues. Based on the available evidence, ESC queried whether there could be a case for reserving REMS for post-menopausal females and/or patients who are eligible for DXA but cannot access it, but noted that any consideration of REMS use in the latter patient group would require reassessment of comparative effectiveness and safety with a different comparator of 'no DXA'. ESC also highlighted that restricting REMS use in this way could itself introduce equity issues. ESC also suggested that it would be helpful to receive further clarification on the types (and number) of patients who would only be able access REMS rather than DXA, and who would only be able to access DXA rather than REMS.

ESC questioned whether failure to complete a REMS scan in practice could lead to co-claiming, as patients with a failed REMS scan would require a subsequent DXA scan (or qCT scan). ESC also considered that patients would be inconvenienced if they require a subsequent scan with a different modality.

ESC noted that, for the economic evaluation, the PICO confirmation agreed that a cost minimisation analysis would be appropriate based on a claim of noninferior safety and noninferior effectiveness compared to DXA. However, ESC noted the appropriateness of this approach is contingent on whether MSAC accepts the claim of noninferior effectiveness and safety has been demonstrated.

ESC noted the applicant developed assessment report (ADAR) presented a simple cost-minimisation approach to the economic analysis that only compared the estimated per service delivery costs for a REMS scan against the MBS fee for a DXA scan, and thus inferred there would be no expectation of a substantial difference in the provision and cost of subsequent healthcare resources. ESC noted the ADAR estimated the REMS per service delivery cost to be \$123.67 but that this included the capital costs for the REMS device. When the capital costs for the REMS device were excluded, the per service delivery cost for REMS was \$99.66, which is similar to the DXA MBS fee of \$106.55 (and the proposed MBS fee for REMS). ESC noted by comparing the cost of REMS to the DXA MBS fee only, the analysis had not considered other costs that may be associated with delivery of the service but not included in the MBS fee (e.g. cost and transport of the mobile form of the device).

ESC noted there was some uncertainty in the estimated cost of \$99.66. ESC noted the commentary had queried the cost per hour assumed for the operator performing the scan and the physician reviewing and reporting on the scan which ESC considered to be low compared to other MBS physician consultation items. Further, there were no data provided to support the



ADAR's estimated 30 minutes per scan although the pre-ESC response stated that this was based on experience using the device in practice. ESC also noted that variations in the estimated rate of 20 scans per week per machine could affect the estimates. ESC noted that device costs are not accepted for inclusion in the MBS fee and that the pre-ESC response clarified that training costs were included in the cost of the device.

ESC noted that a market share approach was used to estimate the financial impact for the proposed MBS listing of REMS, and considered this to be appropriate. ESC also considered it appropriate that each service in a year is assumed to be for a unique patient, and that there are no other MBS costs or cost offsets. ESC noted the ADAR also assumed no growth in DXA usage but did not consider this appropriate, noting the DXA utilisation data were selectively picked from years impacted by the COVID-19 pandemic. The long-term (4-year) utilisation trend shows year-on-year growth in DXA usage. ESC also did not consider the uptake of REMS (estimated by the applicant to be 5–15% of DXA utilisation over 6 years) to be justified or supported by any data in the ADAR. ESC also noted that the ADAR assumed a one-for-one replacement of DXA by REMS at the same MBS fee, yielding a net cost to the MBS budget of \$0 for every year. However, ESC considered the assumption that MBS listing of REMS would not lead to market growth (e.g., uptake in patients eligible for a DXA MBS item but not able to access DXA) to be uncertain. ESC noted that REMS has been available in Italy for 4 years and the experience in Italy could have been presented to provide an indication on the potential uptake of REMS in Australia. ESC also noted information in the commentary that in Italy (where the device is manufactured), there is broader use than that proposed in the ADAR: in addition to diagnosis and limited monitoring, REMS is used in risk stratification and continuity of care for fragility fractures. ESC noted from PASC that use of REMS for fragility scoring was still under development and not ready for clinical use. Consequently, ESC was concerned that there may be potential for REMS to be used outside the indications proposed in the current application. While ESC considered it may be appropriate to assume no impact on other health budgets, it noted that increased diagnosis of osteoporosis could be expected to increase Pharmaceutical Benefits Scheme (PBS) expenditure for osteoporosis treatments.

## **17. Applicant comments on MSAC's Public Summary Document**

The Applicant is disappointed with the MSAC outcome, but equally committed to addressing the concerns and questions raised by MSAC. The Applicant is disappointed by MSAC's appraisal of REMS and considers the non-inferior efficacy and safety of REMS versus DXA was shown by the key studies in the primary, pre-specified outcome analyses. In addition, MSAC acknowledged that both REMS and DXA have the possibility of errors, obtaining invalid scans and therefore the Applicant considers that a direct comparison between the two technologies where there is no absolute known BMD value, should be taken with caution. The Applicant does not believe providing REMS will result in over-servicing of patients, but rather meeting an unmet need by providing a viable option to eligible patients who have never / not recently had a BMD scan. Importantly, the portability of the REMS device (can be as small as a 12kg cabin bag) cannot be considered equivalent to a DXA within a mid-sized bus to meet the unmet need in regional & remote communities. Finally, the Applicant acknowledged the feedback from the societies and will work to address the constructive comments around training and consistency.

## **18. Further information on MSAC**

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