

Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1593.1 – Bioinductive implant for the repair of rotator cuff tear

Applicant: SMITH & NEPHEW PTY LIMITED

Date of MSAC consideration: 1-2 August 2024

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

1. Purpose of application

A re-application requesting listing on the Prescribed List of Medical Devices and Human Tissue Products (PL) of REGENETEN bioinductive collagen implant (BCI) for the repair of rotator cuff tear was received from Smith & Nephew Pty Ltd by the Department of Health and Aged Care (the department). This re-application was linked to a co-dependent PL listing of bovine BCI to be used in surgical repair of rotator cuff tears in conjunction with existing Medicare Benefits Schedule (MBS) items.

MSAC considered the original application (1593) in July 2020 but did not support the proposed listing because of highly uncertain comparative safety and effectiveness of surgical repair with REGENETEN versus surgical repair without REGENETEN. The current re-application aimed to address MSAC's previous concerns. The reason for the original application was in response to an MDHTAC request for a health technology assessment to be conducted on REGENETEN to determine the comparative safety, clinical and cost-effectiveness for inclusion on the PL.

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 for bovine BCI for the repair of partial- or full-thickness rotator cuff tears. MSAC noted the re-application included a single randomised controlled trial (RCT) in patients with partial-thickness tears and two RCTs for full-thickness tears comparing BCI plus surgery versus surgery alone. MSAC noted the re-application did not include a comparison of surgery with BCI against continued conservative management (CM) in the partial thickness tears population. MSAC considered the RCT for partial-thickness tears was limited owing to its small sample size and short average duration of follow-up. MSAC will advise the Medical Devices and Human Tissue Advisory Committee (MDHTAC) that it considered the two new randomised trials for full-thickness tears more reliable than the evidence considered in the previous application for this population however, MSAC did not consider the evidence supported the longer-term claims of superior effectiveness which formed the basis of the economic evaluations, making the estimates of cost-effectiveness uncertain. MSAC also considered the likely uptake and utilisation of BCI were significantly under-estimated.

MSAC advised that a new re-application should focus on functional rather than imaging outcomes. MSAC re-iterated that comparative evidence of effectiveness for BCI against

continued CM in partial-thickness tears should be included in a re-application.

Consumer summary

Smith & Nephew Pty Ltd made an application to the Medical Devices and Human Tissue Advisory Committee (MDHTAC) to list a bovine collagen implant (REGENETEN) on the Prescribed List (PL) to repair rotator cuff tears. The MDHTAC requested that MSAC perform a health technology assessment for REGENETEN to determine its comparative effectiveness, safety and cost-effectiveness.

The rotator cuff is a common name for the group of four muscles and their tendons in the shoulder. The rotator cuff starts on the shoulder blade, extending over the shoulder, with the tendons anchoring on the upper arm bone and surrounding the ball of the shoulder like a cuff—hence the term rotator cuff. The rotator cuff muscles are known as stabilising muscles, because they hold the ball of the shoulder in the socket properly when a person moves their arm, by balancing the forces of the bigger shoulder muscles. Damage to the rotator cuff, such as from a torn tendon, can cause symptoms such as shoulder pain and weakness. Rotator cuff tears can happen during an acute injury or trauma (e.g. fall on the arm while running), or can occur gradually which is called a chronic tear. Chronic tears are common as people age, as the tendons can degenerate and fray, and sometimes tears don't cause any symptoms at all.

This application was for use of REGENETEN during surgical repair of chronic rotator cuff tears classified as 'full thickness' or 'partial' in people who continue to have symptoms after 3 months of conservative treatment (e.g., pain relief medications, physiotherapy) The application did not include people who had acute tears, or for people who did not have any symptoms.

REGENETEN is implanted during shoulder surgery to provide a layer of collagen over an injured tendon. It is intended to provide a base on which the body can grow new tissue to repair the tendon.

MSAC noted that the application presented three new randomised controlled trials, one recruited patients with partial tears and two recruited patients with full tears. MSAC noted that all three trials compared surgical repair using REGENETEN versus surgical repair alone. For the population with partial tears, MSAC noted that the application did not present any evidence that compared surgical repair using REGENETEN with conservative management. MSAC considered the single trial in partial tear provided limited information on effectiveness as not many patients were included and the results available were of short-term follow-up. While MSAC considered the two new trials in patients with full tears of better quality than the evidence presented in the original application, MSAC considered the evidence presented insufficient to show that using REGENETEN would result in better recovery or outcomes for patients, such as improved function or less pain.

Because the effectiveness and safety were uncertain, MSAC could not say whether adding REGENETEN to standard surgical repair represents better value for money than standard surgical repair alone.

MSAC's advice to the Medical Devices and Human Tissue Advisory Committee (MDHTAC)

MSAC advised the MDHTAC that REGENETEN's comparative effectiveness, safety and value for money were all uncertain due to uncertain benefit in patient-related functional outcomes and over the long-term, making it difficult to decide if surgical repair using REGENETEN would represent value for money.

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

MSAC noted that a re-application requesting listing on the PL of REGENETEN BCI for the repair of rotator cuff tear was received from Smith & Nephew Pty Ltd by the Department of Health and

Aged Care. This re-application was linked to a codependent application to include bovine BCI on the PL and for it to be used in surgical repair of symptomatic rotator cuff tears in conjunction with existing MBS items.

MSAC recalled that it had previously considered bovine BCI (REGENETEN; application 1593) for the repair of rotator cuff tear in July 2020 but did not support public funding at that time because the evidence for comparative safety, effectiveness and cost-effectiveness was highly uncertain relative to standard surgical repair in both subpopulations, that is, population 1: patients with partial-thickness rotator cuff tears (PTRCT) and population 2: patients with full-thickness rotator cuff tears (FTRCT).

MSAC noted that all the individual consultation feedback received was from medical specialists and was overall supportive of the application. The organisational feedback noted concerns from private health insurers regarding the increase to private health insurance premiums, uncertainty of value and potential for service leakage.

MSAC noted the applicant presented new evidence (3 randomised controlled trials (RCTs)) for using bovine BCI to repair PTRCT and FTRCT. For population 1 (PTRCT), 2 RCTs were presented: Wang et al. 2023 (unpublished 7-page clinical study report [CSR]) and Camacho-Chacon et al. 2023 (unpublished 2023 CSR, pre-proof 2024 paper). For population 2 (FTRCT), one RCT (Ruiz Iban et al. 2023) was presented.

MSAC noted that the Wang 2023 trial had a small sample size (N = 29), included patients with symptomatic high-grade PTRCT based on magnetic resonance imaging (MRI) scans and reported short-term follow-up results (3 months). MSAC noted that the Camacho-Chacon 2023 trial was a single surgeon trial which included patients with supraspinatus full-thickness tear and was designed to evaluate tendon integrity following surgical treatment for FTRCT. MSAC considered it inappropriate to use the Camacho-Chacon 2023 trial as evidence for PTRCT and was concerned that the trial might not reflect actual clinical practice.

In addition to these RCTs, the ADAR provided safety and effectiveness evidence based on other clinical trials identified in the applicant's systematic literature search. MSAC noted that there are ongoing studies relevant to rotator cuff repair, including but not limited to the Australian Rotator Cuff (ARC) Study¹. MSAC noted the ARC study is expected to be completed in 2026.

MSAC noted that the re-application did not include continued CM as an additional comparator for population 1, as advised by the PICO Advisory Sub-committee (PASC) in August 2023. MSAC noted PASC's consideration of the natural history of rotator cuff tears, where the tears may resolve spontaneously in a proportion of patients who delay surgery. MSAC noted PASC's concern that the proposed listing, if approved, might reduce the threshold for surgery for rotator cuff tears in population 1 and therefore result in some proportion of patients who might otherwise have continued with CM opting for surgery instead. MSAC noted the applicant's reiteration of its reasons against continued CM in its pre-MSAC response. MSAC agreed with its Evaluation Sub-committee (ESC) that population 1 should have been compared with continued CM as well as surgery, although noted the challenges in collecting unconfounded data on CM or natural history.

MSAC noted that the proposed clinical management algorithm deviated from the clinical management algorithm confirmed by PASC. The ADAR claimed that the PASC-confirmed clinical management algorithm did not reflect the possibility of patients who improve after conservative

¹ The ARC study is a randomised controlled Australian trial that evaluates arthroscopic surgery with repair of the rotator cuff versus arthroscopic surgery without rotator cuff repair, in patients with shoulder pain and rotator cuff tears. The trial aims to find out if repairing the rotator cuff makes a difference to shoulder pain and function. The study was funded by the Whitlam Orthopaedic Research Centre, a not-for-profit organisation (available: <https://www.arcstudy.org/>).

management relapsing at some point in time and re-entering the treatment algorithm. However, MSAC noted that the Commentary considered that the PASC-confirmed algorithm did include a treatment arm for patients who improve post-CM relapse and return to the “no improvement stage” and following the treatment pathways. By contrast, the applicant-amended algorithm included the relapsed patients going back to the start of the treatment algorithm. The Commentary considered that the relapsed CM patients did not require re-establishment of evidence of cuff disease, hence the pathway proposed in the PASC algorithm for CM relapse patients would be more appropriate.

Overall, for population 1 MSAC considered that the clinical claim of superior effectiveness and noninferior safety compared to treatment with standard surgical repair was uncertain due to there being only one study, with a small sample size, and lack of long-term follow-up. Additionally, MSAC agreed with ESC that the study population of Camacho-Chacon et al., (2023)² increased uncertainty in the clinical claim for partial tears patients as it included FTRCT patients. MSAC further noted that the re-application did not present evidence to support the correlation between radiographic outcomes and functional outcomes. MSAC agreed with ESC that whilst correlational evidence was important in theory, especially when re-tears can be asymptomatic and that there was no evidence that avoidance of re-tears is associated with better clinical outcomes, it was aware that such correlational evidence is unlikely to exist or be forthcoming. Consequently, MSAC noted this further emphasises the need for RCTs with non-radiological measures as primary outcomes.

For the FTRCT population (population 2), MSAC considered the clinical claim of superior effectiveness and noninferior safety compared to treatment with standard surgical repair was uncertain. While MSAC considered the two new randomised trials for full-thickness tears more reliable than the evidence considered in the previous application for this population, MSAC noted the Ruiz Iban (2023) trial showed superiority in imaging-based outcomes such as retear rates but no significant differences in patient-reported outcomes (PROs) compared to standard of care (surgery without augmentation). MSAC considered that the claim of non-inferiority in comparative safety was likely but uncertain due to limited long-term safety data. MSAC noted that the applicant’s pre-MSAC response presented a conference abstract containing 2-year data from the Ruiz Iban study. MSAC noted there was some evidence that in the FTRCT population use of BCI reduced imaging-based retear rates at 12 months, compared to standard surgery, and may improve return to work.

Regarding the economic evaluation, MSAC noted that the re-application used the Camacho-Chacon 2023 trial to inform the economic evaluation for population 1 and the Ruiz Iban 2023 trial for population 2. However, MSAC noted that neither of these trials were conducted in Australia which might affect their applicability to Australian clinical practice.

MSAC noted that for population 1 (PTRCT), the ADAR presented a cost-effectiveness analysis, with the health outcomes expressed as the incremental cost per ‘change in the minimal clinical important difference’ (MCID; defined as 15.5 points in the ASES score). MSAC considered that whilst it was reasonable to conduct a cost-effectiveness analysis for the PTRCT population, the denominator for the incremental cost-effectiveness ratio (ICER) was difficult to interpret and would have been more meaningful if it had been expressed as the incremental cost per responder (with responder status determined by achievement of the MCID). MSAC noted the ADAR reported that using REGENETEN in patients with symptomatic PTRCT who have failed at least 3 months of CM had an ICER of **redacted** per change of 15.5 points in the ASES score.

² Camacho-Chacon JA et al., Bioinductive collagen implants facilitate tendon regeneration in rotator cuff tears. *J Exp Orthop.* 2022 Jun 8;9(1):53.

MSAC noted that in the re-specified base-case considered by ESC, the incremental benefit became 0.465 per change of 15.5 points in the ASES score and the ICER became **redacted** per change of 15.5 points in the ASES score.

MSAC noted that for population 2 (FTRCT), the ADAR provided a cost-utility analysis, with the health outcomes expressed in quality-adjusted life years (QALYs) gained. MSAC noted the Commentary considered the population, outcomes and the type of economic analysis were appropriate. MSAC also considered the perspective and discount rate were appropriate for both subpopulations however, MSAC agreed with ESC that it was inappropriate to extrapolate to a 5-year time horizon from the evidence available. MSAC noted that the base case ICER for population 2 (FTRCT) was **redacted** /QALY. The key drivers of the model for population 2 were retear rates, the utility value applied to CM after a tear fails to heal, and the cost of the BCI kit, all of which MSAC considered to be uncertain. MSAC considered that the model should include downstream costs of non-surgical management. MSAC noted that the ADAR estimated total savings to the MBS of \$0.12 million in Year 1, rising to \$0.90 million in Year 6, due to a reduced rate of retear.

MSAC noted that the estimated cost to private health insurers (PHIs) to fund REGENETEN is expected to grow from around **redacted** in Year 1 to **redacted** in Year 6. Considering cost-offsets, net costs to PHIs are expected to reach \$1.4 million in Year 1 and rise to \$8.7 million in Year 6. Offsets to PHIs are expected to reduce the total costs by around **redacted** in Year 6. MSAC considered that the financial estimates were uncertain and that the likely uptake and utilisation of BCI was significantly underestimated.

MSAC noted the applicant's agreement in its pre-MSAC response to add a limit to the PL listing (restriction to once per shoulder) and/or to create an MBS item number for REGENETEN. MSAC agreed with the department that it is important to prevent leakage, especially considering that REGENETEN is already being used in other parts of the body in clinical trials. MSAC agreed with the department and considered it appropriate to restrict the use of REGENETEN to once per shoulder per lifetime. MSAC also noted the applicant had expressed a willingness to discuss restricting the use of REGENETEN to a narrower patient population, e.g., full thickness tears, until further evidence on partial tears become available.

MSAC noted that an expedited pathway via ESC then MSAC for a re-application based on the current ratified PICO confirmation would be appropriate. MSAC considered that a re-application to MSAC should address the outstanding issues raised in the PSD, including but not limited to the following to address remaining key areas of uncertainty:

- Provide RCT evidence with non-radiological measures as primary outcomes.
- Provide evidence on the comparative safety, clinical and cost-effectiveness of surgical repair using BCI against continued CM in partial-thickness tears.
- Consider a focus on the clinical claim that REGENETEN reduces time to recovery.
- Consider respecifying the economic evaluation for FTRT with the inclusion of appropriate downstream costs, use of trial-based or time trade-off utility weights and shortening the time horizon to 1 year (as retear rates were only available at 12 months).

4. Background

MSAC previously considered REGENETEN bovine BCI for the repair of rotator cuff tear in July 2020 (MSAC application 1593). MSAC did not support public funding for bovine BCI (at that time, and advised the Prostheses List Advisory Committee (PLAC; now the Medical Devices and Human Tissue Advisory Committee) that the evidence for comparative safety, effectiveness and cost-

effectiveness was highly uncertain relative to standard surgical repair in both subpopulations (i.e., Population 1: patients with partial-thickness rotator cuff tears (PTRCT) and Population 2: patients with full-thickness rotator cuff tears (FTRCT)³. The key matters of concern from the previous MSAC consideration in July 2020 and how they have been addressed in the current re-application are provided in Table 1.

Table 1: Summary of key matters of concern in the previous and current applications

Component	Matter of concern in the previous application (MSAC 1593, July 2020 MSAC meeting)	How the current re-application (MSAC 1593.1) addressed it
Clinical evidence	MSAC considered that the applicant would need to provide high quality evidence before they could resubmit to MSAC (pg4, PSD for MSAC application 1593, July 2020 MSAC meeting).	Partially addressed. The ADAR removed case study data and naïve indirect comparisons from the evidence base as advised by MSAC, and provided comparative effectiveness and safety based on three new RCTs.
	MSAC and ESC noted that the ADAR relied on low-quality evidence from naïve indirect comparisons for the comparative effectiveness and safety of REGENETEN versus standard surgery in both populations (pg2, PSD for MSAC application 1593, July 2020 MSAC meeting).	For Population 1: patients with symptomatic PTRCT, the ADAR provided evidence from the PROCTOR Trial (Wang et al., 2023) and Camacho-Chacon et al., 2023 RCTs. The PROCTOR Trial provided only interim results for 29 patients with followed up of three months.
	MSAC noted the upcoming cohort study that would provide comparative evidence of REGENETEN vs. standard surgery in PTRCT (NCT03734536) (pg4, PSD for MSAC application 1593, July 2020 MSAC meeting).	Also, the commentary considered that the Camacho-Chacon et al., 2023 RCT was not relevant for Population 1 as the study population was patients with FTRCT. For Population 2, the ADAR provided evidence from the published Ruiz Ibán et al., 2023 trial and this trial was relevant for Population 2. The HIGHPATH cohort study (NCT03734536)* was not presented as it was terminated by the sponsor due to business reasons not related to patient safety. The commentary noted several issues in the clinical evidence provided in the ADAR and these were discussed in detail in relevant sections. Thus, the commentary considered that the clinical evidence provided in this ADAR was also uncertain.
	REGENETEN studies had small sample sizes (pg2, PSD for MSAC application 1593, July 2020 MSAC meeting).	Partially addressed. The ADAR provided evidence based on the three new RCTs with following sample sizes: Wang et al.,2023 - Sample size of 29 Camacho-Chacon et al.,2023 - Sample size of 60 Ruiz Ibán et al.,2023 - Sample Size of 124
	MSAC noted that the naïve indirect comparisons did not have a common comparator and were not adjusted (pg2-3, PSD for MSAC application 1593, July 2020 MSAC meeting).	Addressed. Data presented in the ADAR from 3 RCTs that provided direct comparison with standard of care (i.e. surgery).
	MSAC also noted that the imaging results were problematic due to the lack of definitions for “re-tear,” “incomplete healing” and “treatment failure” (pg3, PSD for MSAC application 1593, July 2020 MSAC meeting).	Partially addressed. The literature suggests that there is still controversy around the lack of definition for “re-tear,” “incomplete healing” and “treatment failure”. The ADAR approximated “tear fail to heal” to “re-tear rate” reported in RCTs. Of note, the ADAR did not
	MSAC considered using imaging results as the	

³ Public Summary Document, MSAC Application No. 1593 – Bovine bioinductive collagen implant (REGENETEN™) for repair of rotator cuff tear

Component	Matter of concern in the previous application (MSAC 1593, July 2020 MSAC meeting)	How the current re-application (MSAC 1593.1) addressed it
	primary outcome to be inappropriate, as there is no evidence to support correlating imaging results to PROs, or to predict a reduced rate of osteoarthritis (pg3, PSD for MSAC application 1593, July 2020 MSAC meeting).	provide justification for using “tear fail to heal” as “retear rate”. However, the commentary identified this as in line with the literature**.
	MSAC and ESC considered the core outcomes (pain reduction, function and adverse events) to be the most important outcomes (pg3, PSD for MSAC application 1593, July 2020 MSAC meeting).	Further, the ADAR provided evidence related to retear rates based on the industry standard Sugaya scoring system to assess imaging results. The Sugaya classification is the most common system used to evaluate rotator cuff repair.
	ESC and MSAC noted that the clinical claim of superior effectiveness was only supported for imaging outcomes rather than functional outcomes.	No evidence was provided to support correlating imaging results with patient-reported outcomes.
	Adverse events were not reported in the studies for standard surgery in patients with FTRCTs (pg3, PSD for MSAC application 1593, July 2020 MSAC meeting).	The ADAR provided evidence related to pain reduction, function and adverse events based on RCTs.
	MSAC and ESC noted limited long-term AEs (11 patients followed over 5 years); with no long-term adverse event data for use of REGENETEN in FTRCT patients. ESC also noted the clinical claim of non-inferiority in comparative safety for sub-Population 2 was not supported by statistically significant higher revision surgery rates.	The evidence suggests superiority of effectiveness in imaging-based outcomes such as retear rates. However, no significant differences were reported in improvement in patient-reported outcomes between groups for patients with FTRCTs.
	MSAC noted the systematic review and meta-analysis which concluded that structural integrity of the rotator cuff after repair does not correlate with clinically important differences in validated functional outcome scores (pg3, PSD for MSAC application 1593, July 2020 MSAC meeting).	The interim results from the Wang et al., 2023) trial was based on three months follow up. The Camacho-Chacon et al., 2023 results were based on two-year follow up. The Ruiz Ibán et al.,2023 follow up was only one year. Therefore, long-term safety and effectiveness were uncertain. The ADAR provided comparative safety evidence other than revision surgery rates based on Ruiz Ibán et al.,2023 RCT for Population 2.
	ESC noted minor differences regarding the removal of footnotes in the ADARs clinical algorithm compared with the Ratified PICO confirmation algorithm.	Partially addressed. The ADAR claimed that failed tendon healing was associated with reduced strength and function, especially in the longer term, based on single arm clinical trials. However, the ADAR provided evidence of superiority of effectiveness in imaging-based outcomes such as retear rates in Population 2. However, there were no significant differences in clinical outcomes or in validated functional outcome scores.
	<p data-bbox="193 1715 343 1973">Clinical claim</p> <p data-bbox="343 1715 874 1973">MSAC noted that the pooled risk of revision of surgery rates was statistically significantly higher for REGENETEN for FTRCTs (0.069 vs. 0.027 for standard surgery). MSAC noted that the same risk was higher for standard surgery than for REGENETEN for PTRCTs (0.018 vs. 0.078 for standard surgery) (pg3, PSD for MSAC application 1593, July 2020 MSAC meeting).</p> <p data-bbox="343 1973 874 2036">MSAC noted that there were no statistically significant differences in the pooled risk for core</p>	Not addressed There were minor differences in the clinical algorithm with the Ratified PICO confirmation algorithm in resubmission ADAR (MSAC application 1593.1) as well and the ADAR provided justifications for the deviations. The commentary considered these deviations were not appropriate.

Component	Matter of concern in the previous application (MSAC 1593, July 2020 MSAC meeting)	How the current re-application (MSAC 1593.1) addressed it
	functional outcomes for REGENETEN and standard surgery for either population over 12–24 months follow-up (pg3, PSD for MSAC application 1593, July 2020 MSAC meeting).	et al., 2023 and Camacho-Chacon et al, 2023 studies reported better PROs for the REGENETEN group, however, Wang et al., 2023 had only three months follow up and Camacho-Chacon et al, 2023 was not relevant for this population.
	MSAC considered that the results trended towards better PROs for standard surgery (pg3, PSD for MSAC application 1593, July 2020 MSAC meeting).	For FTRCT, the Ruiz Ibán et al., 2023 trial did not report significant improvement in PROs between groups.
Economic evaluation	MSAC noted that the uncertainties in clinical effectiveness led to key uncertainties in the economic evaluation, because very low-quality evidence was used to inform the key model inputs (pg3, PSD for MSAC application 1593, July 2020 MSAC meeting).	Partially addressed. The ADAR provided two new economic models for the two populations based on published literature including two new RCTs, one for Population 1 (PTRCT), Camacho-Chacon et al, 2023, and one for Population 2 (FTRCT), Ruiz Ibán et al.,2023. These models differed from the previous application. However, the commentary noted several issues with the economic evaluations, and these are discussed in detail in the relevant sections.
	The economic model assumes non-inferior safety, which is uncertain, and superior functional outcomes, for which there is no evidence (pg3, PSD for MSAC application 1593, July 2020 MSAC meeting).	Partially addressed. The ADAR addressed these issues. However, the commentary considered the safety and effectiveness evidence is still uncertain due to; <ul style="list-style-type: none"> • the Camacho-Chacon et al, 2023 trial not being relevant for Population 1 and the effectiveness measure calculations (i.e., average improvement in ASES score over time) in the model not being accurate. • In the Population 2 economic model, the health state utilities and transition probabilities were not relevant.
	MSAC considered it inappropriate that the ADAR model relied heavily on imaging outcomes (pg3, PSD for MSAC application 1593, July 2020 MSAC meeting).	Partially addressed For Population1, the main effectiveness measure was based on the ASES score, which is a functional score. However, for Population 2, the retear rates were assessed by MRI.
	MSAC also agreed with ESC, which noted several other structural issues with the model (pg3, PSD for MSAC application 1593, July 2020 MSAC meeting).	Partially addressed A new model had been developed and presented for both populations with a time horizon of two years. For PTRCT, a cost effectiveness analysis was presented using a decision tree model with change in 'MCID' (defined as a 15.5 point change in the ASES score) as an outcome measure. Of note, the health outcome was sourced directly from an RCT(Camacho-Chacon et al., 2023), which was not relevant for this population. For FTRCT, a cost utility analysis was presented using a decision tree model that was based on a recent publication by McIntyre et al., 2023 and the model was modified to include QALYs as the health outcome.
	ESC noted a heavy reliance on expert opinion added significant uncertainty to the original economic evaluation submitted in the previous	Addressed. The ADAR did not use expert opinion in the economic evaluation (The expert opinion and

Component	Matter of concern in the previous application (MSAC 1593, July 2020 MSAC meeting)	How the current re-application (MSAC 1593.1) addressed it
	ADAR.	qualitative research quotes, to validate findings in published literature, presented only in the clinical evidence section).
Financial impact	MSAC and ESC considered the ADAR's original estimate of prevalence of PTRCT (71%) vs. FTRCT (29%) to be uncertain (pg4, PSD for MSAC application 1593, July 2020 MSAC meeting).	Addressed. The proportion of PTRCT and FTRCT was based on an Australian cohort study Yeo et al., 2017, which reported 39% PTRCT and 61% FTRCT among 1624 patients who had undergone arthroscopic rotator cuff repair.
	MSAC noted that the financial impact presented in the commentary, which was re-calculated using costs to private payers and inclusion of costs related to other items (MBS) and showed that the total budget impact may be 20% higher in the respecified base case financial model than that presented in the ADAR (pg4, PSD for MSAC application 1593, July 2020 MSAC meeting).	Partially addressed. The ADAR presented a new budget impact model. However, the commentary noted financial estimates were uncertain due to: <ul style="list-style-type: none"> • The incidence rate for the rotator cuff repair in the Australian population was based on incidence data reported for the year 2011 based on a Finland national registry study. • The ADAR assumed an annual increase of redacted in the uptake of rotator cuff repairs for REGENETEN. • The data used to calculate the percentage of patients receiving different management options after retear i.e., revision of rotator cuff tear repair, reverse total shoulder arthroplasty and CM were not relevant for the calculations.
MBS items do not restrict access	The ADAR was based on a once-only graft, but its use is not restricted in any form on the MBS. Hence, leakage could be an issue, or it could be used multiple times (although there is no evidence for this). Private insurers may want to stipulate limits on use (e.g. once per lifetime).	Concern remained. PASC for the current reapplication noted the applicant stating its willingness to work with the relevant authorities to ensure a "once-per-shoulder" restriction (MSAC 1593.1 Ratified PICO Confirmation, pg10-11). The ADAR stated that "REGENETEN is considered to be a 'once-only' procedure per tendon". No further details provided in the ADAR other than stating that conventional surgery may be an option if REGENETEN fails on the first attempt. There is a difference in costs between receiving the proposed device once per lifetime, once per shoulder and once per tendon, with potential flow-on impact on downstream costs and consequences.

Source: Table 8 of pg22-23, Table 9 of pg23 and Table 10 of pg23-24 of the MSAC application 1593.1 ADAR + inline commentary; pg26 of PSD for MSAC 1593, July 2020 MSAC meeting.

Abbreviations: ADAR = Applicant developed assessment report; AE = adverse event; ASSES = American Shoulder and Elbow Society; CM = conservative management; CSR = clinical study report; ESC = Evaluation subcommittee; FTRCT = full-thickness rotator cuff tears; MBS = Medicare Benefits Schedule; MSAC = Medical Services Advisory Committee; MRI = magnetic resonance imaging; MCID = Minimum clinically important difference; PICO = Population Intervention Comparator Outcome; PRO = patient-reported outcomes; PTRCT = partial-thickness rotator cuff tears; PSD = Public Summary Document; RCT = Randomised controlled trial; QALY = Quality adjusted life years.

Notes: *this study was previously noted by PASC, and it was one of the three studies, which Therapeutic Goods Administration required updates on for the Australian Register of Therapeutic Goods entries 340095 and 340096

**This approach was used in McIntyre et al.,2023 study.

For the Applicant Developed Assessment Report (ADAR), the applicant requested an expedited pathway assessment as the proposed PICO was closely aligned to the previously Ratified PICO confirmation (September 2019). The department sought MSAC Executive advice for the progression of the planned ADAR. At its 21 April 2023 meeting, the MSAC Executive advised that consideration by PASC was required to confirm the PICO for the ADAR particularly to define the duration of failure to CM) in the eligible population and whether to consider continued CM as an additional comparator in Population 1 (PTRCT) due to the intervention being used without standard surgical repair (MSAC 1593.1 Ratified PICO confirmation, pg5-6).

5. Prerequisites to implementation of any funding advice

The REGENETEN Bioinductive implant is a Therapeutic Goods Administration (TGA) approved Class III Medical Device and has been on the Australian Register of Therapeutic Goods (ARTG) since 24th July 2020. The intended purpose for REGENETEN as per the ARTG entry (ARTG ID: 340095 - REGENETEN Arthroscopic Bioinductive Implant and ARTG ID 340096 - REGENETEN Mini-Open Bioinductive Implant) is for the management and protection of tendon injuries.

A third entry from the same sponsor (ARTG ID 384118 - Bioinductive Implant with Arthroscopic Delivery System, effective date 16 February 2022) with the same GMDN has an additional intended purpose:

- The REGENETEN Bioinductive Implant is indicated for the management and protection of rotator cuff injuries in which there has been no substantial loss of tendon tissue.

The entry has the following specific conditions: The sponsor must provide the TGA the study "Clinical Trial on the Effect of REGENETEN Bioinductive Implant in the Supraspinatus Tendon Repair (NCT04444076)"⁴ within three months of the clinical trial's completion.

The device is currently available in Australia and there are currently no prerequisites to implement funding advice.

6. Proposal for public funding

This ADAR was for a PL listing of REGENETEN for use in the surgical repair of rotator cuff tears in conjunction with existing MBS items. Consistent with the Ratified PICO confirmation, and as agreed by PASC, there are already relevant and clinically appropriate MBS items available that would allow the use of REGENETEN if the product obtains a listing on the PL. PASC considered MBS item 48960 the most applicable item amongst the three MBS items (MBS items 48960, 48906 and 48909) proposed by the applicant (MSAC 1593.1 Ratified PICO confirmation, pg25), given it refers to arthroscopic repair, which is more common over mini-open technique. Of note, 'mini-open' and arthroscopic rotator cuff surgical repair techniques attract the same MBS fee (MBS item 48960), though evidence⁵ suggests that arthroscopy is more expensive and requires more operative time than the 'mini-open' technique (MSAC 1593.1 Ratified PICO confirmation pg25).

Orthopaedic surgeons perform the procedure. Therefore, no additional training is required by the surgeon to use REGENETEN in appropriate patients.

⁴ Clinical Trial on the Effect of REGENETEN Bioinductive Implant in the Supraspinatus Tendon Repair. (MALLAMANGUITO) study expected completion date will be February 2026.

⁵ Oliva, F., E. Piccirilli, M. Bossa, A. G. Via, A. Colombo, C. Chillemi, G. Et al., (2015). "I.S.Mu.L.T - Rotator Cuff Tears Guidelines." *Muscles Ligaments Tendons J* 5(4): 227-263.

As noted in MSAC 1593.1 Ratified PICO confirmation, Table 2 summarised the existing MBS items relevant for this application.

Table 2: Presentation of existing MBS items relevant for the application

Category 3 THERAPEUTIC PROCEDURES
MBS item 48960 SHOULDER, reconstruction or repair of, including repair of rotator cuff by arthroscopic, arthroscopic assisted or mini open means*; arthroscopic acromioplasty; or resection of acromioclavicular joint by separate approach when performed - not being a service associated with any other procedure of the shoulder region (H) Multiple Operations Rule (Anaes.) (Assist.)
Fee: \$1,036.25 Benefit: 75% = \$777.20
APPLICANT
Prescribed List rebate: bovine BCI (REGENETEN)
Fee: redacted Benefit: redacted
Category 3 THERAPEUTIC PROCEDURES
MBS item 17610 ANAESTHETIST, PRE-ANAESTHESIA CONSULTATION (Professional attendance by a medical practitioner in the practice of ANAESTHESIA) - a BRIEF consultation involving a targeted history and limited examination (including the cardio-respiratory system) - AND of not more than 15 minutes duration, not being a service associated with a service to which items 2801 - 3000 apply
Fee: \$48.05 Benefit: 75% = \$36.05 85% = \$40.85
Category 3 THERAPEUTIC PROCEDURES
MBS item 21622 INITIATION OF MANAGEMENT OF ANAESTHESIA for arthroscopic procedures of shoulder joint (5 basic units)
Fee: \$109.00 Benefit: 75% = \$81.75 85% = \$92.65
Category 3 THERAPEUTIC PROCEDURES
MBS item 17615 Professional attendance by a medical practitioner in the practice of anaesthesia for a consultation on a patient undergoing advanced surgery or who has complex medical problems, involving a selective history and an extensive examination of multiple systems and the formulation of a written patient management plan documented in the patient notes - and of more than 15 minutes but not more than 30 minutes duration***, not being a service associated with a service to which items 2801 - 3000 apply
Fee: \$95.60 Benefit: 75% = \$71.70 85% = \$81.30
Category 3 THERAPEUTIC PROCEDURES
MBS item 51303 Assistance at any operation mentioned in an item in Group T8 that includes "(Assist.)" for which the fee exceeds \$614.55 or at a series or combination of operations mentioned in an item in Group T8 that include "(Assist.)" for which the aggregate fee exceeds \$614.55 one fifth of the established fee for the operation or combination of operations
Fee: \$207.25**** Benefit: 75% = \$155.44 85% = \$176.16

Source: Table 17, pg65-66 of MSAC 1593.1 ADAR+ in-line commentary; fees were updated based on current MBS item fees on the MBS (MBS online) (accessed 2 April 2024)

Abbreviations: BCI= bioinductive collagen implant; MBS=Medicare Benefits Schedule.

Notes: * This approach is also included in MBS item 48960 (i.e., same MBS fee/rebate for arthroscopic or mini-open technique).

** Prescribed List rebate: bovine BCI (REGENETEN) was **redacted** in the MSAC 1593.1 Ratified PICO confirmation.

*** Applicant advised that the estimated time of the surgical procedure (application of REGENETEN) is 15-30 minutes. MBS item 23010 included in the MSAC 1593.1 ratified PICO confirmation is relevant for the procedures related to less than 15 minutes. Therefore, the ADAR included relevant MBS item 17615 instead of 23010 based on the procedure time of 15-30 minutes.

****Calculated based on the one fifth of the fee for the MBS item 48960

The ADAR included MBS item 17615 based on the procedure time of 15-30 minutes instead of MBS item 23010 mentioned during the Ratified PICO confirmation. *ESC considered that both anaesthesia consultation (MBS item 17615) and anaesthesia items (MBS 23010, 23025, 23035 depending on the length of anaesthesia) may be associated with the surgical repair. ESC noted that these items were not directly used in the economic evaluation of either population.*

MSAC was previously concerned that the proposed device, intended as once-only use, might be used multiple times and considered the potential leakage issue might be mitigated by the private health insurers imposing limits on usage (e.g., once per lifetime) (pg26 of PSD for MSAC 1593, July 2020 MSAC meeting).

PASC for the current reapplication noted the applicant stating its willingness to work with the relevant authorities to ensure a “once-per-shoulder” restriction (MSAC 1593.1 Ratified PICO Confirmation, pg10-11). The ADAR stated that “REGENETEN is considered to be a ‘once-only’ procedure per tendon”. No further details provided in the ADAR other than stating that conventional surgery may be an option if REGENETEN fails on the first attempt. There is a difference in costs between receiving the proposed device once per lifetime, once per shoulder and once per tendon, with potential flow-on impact on downstream costs and consequences.

7. Population

There were 2 PICO sets, with 2 distinct populations based on the depth of the rotator cuff tear:

- Population 1 (PICO set 1): Patients with symptomatic PTRCT where there is no substantial loss of tendon tissue and who have failed at least three months of non-surgical CM and are considered eligible for (or indicated for) surgical repair.
- Population 2 (PICO set 2): Patients with symptomatic FTRCT where there is no substantial loss of tendon tissue and who have failed at least three months of non-surgical CM and are considered eligible for (or indicated for) surgical repair.

The current approaches to surgical management differ based on thickness of the rotator cuff tear i.e., PTRCT or FTRCT.⁶ PTRCT do not extend through the full thickness of the tendon, whereas FTRCT extends the full detachment of the tendon that attaches the muscles from the shoulder blade to the head of the humerus. The bovine BCI will be performed in addition to arthroscopic surgery (debridement and bursectomy) in Population 1 and in addition to standard arthroscopic or mini-open surgical repair in Population 2.

Patients with symptomatic PTRCT or FTRCT should fail CM (i.e., pain relief, modified daily activities and physical therapy) for at least three months to become eligible for surgery. PASC noted that according to clinician advice, the time from first onset of symptoms to presentation to an orthopaedic surgeon was highly variable. However, it was agreed that that the time frame of a minimum of three months of CM was reasonable given the variable nature of rotator cuff tears.

The ADAR provided amended current and proposed clinical management algorithm, which was deviated from the PASC suggested clinical management algorithm. PASC algorithm implied that patients who were part of the ‘no surgery’ group, would then go on to receive arthroscopic surgery at some point in time. The ADAR highlighted that it was not practical or feasible for a patient who at one point opted for ‘no surgery’ to then receive arthroscopic or mini open surgery (with or without BCI) as it was unlikely that patients who would choose to continue with CM would opt to receive the proposed intervention. The ADAR claimed that the clinical management

⁶ Bokor DJ, Sonnabend D, Deady L, Cass B, Young A, Van Kampen C, et al. Preliminary investigation of a biological augmentation of rotator cuff repairs using a collagen implant: a 2-year MRI follow-up. 2015;5(3):144.

algorithm did not reflect the possibility of patients who improve post CM relapse at some point in time and restart the treatment algorithm. However, the commentary considered that the PASC suggested algorithm already included a treatment arm for patients who improve post CM relapse at some point in time going back to the 'no improvement stage' and following the treatment pathways, whereas the amended algorithm included the relapse patients going back to the start of the treatment algorithm. The commentary considered that the relapsed CM patients did not require establishment for evidence of cuff disease as it was already established, hence the pathway proposed in the PASC algorithm for CM relapse patients would be more appropriate.

8. Comparator

Standard surgical repair (take-down and repair - i.e., suture anchors alone, without use of REGENETEN) was the nominated comparator in the ADAR for both Population 1 (PTRCT) and Population 2 (FTRCT). It is the current standard of care for patients who failed CM (not responded to pain relief, modified daily activities and physical therapy) for 3 months and are eligible for surgical repair. The comparator is currently funded by the MBS (Please refer to Table 2 for the existing MBS item relevant for the comparator (as well as the intervention)).

At the PASC meeting in August 2023, it was proposed to include continued CM without surgical repair as an additional comparator in Population 1, given that the introduction of the implant may reduce the threshold for surgery among patients who opt for CM due to the lower burden of rehabilitation post-surgery (MSAC 1593.1 Ratified PICO confirmation, pg16). The ADAR deviated from PASC's recommendation to include continued CM as an additional comparator for Population 1.

The ADAR argued that the target population are those who have experienced significant impact to their quality of life (QoL) as a result of the symptomatic nature of their tear, and upon failing non-surgical management, have requested further intervention via surgical means. The ADAR stated that it does not make practical sense for a patient who is eligible and indicated for, and who is willing to and has provided consent to undergo surgical repair based on surgeon recommendation to instead continue CM post failure. It further claimed that evidence from the studies and expert opinion suggested that of those PTRCT patients who do not improve after initial conservative treatment, some will progress to full-thickness tears, and their condition commonly worsens or shows no significant improvement in signs and/or symptoms upon clinical re-evaluation. The ADAR argued that it is unethical and inappropriate to randomise symptomatic patients despite CM failure to a no-surgery arm of a trial. The commentary considered that it is still appropriate to consider continued CM as a comparator for patients who do not opt for surgical treatment (e.g., personal preference) as per the proposed algorithm. In terms of ethics, the commentary noted that there are studies that have evaluated non-surgical and surgical treatments for rotator cuff disease, which reported no significant difference in outcomes in surgical treatments compared to continued CM among patients with rotator cuff tears ^{7,8}.

⁷ Anssi Ryösä, Katri Laimi, Ville Äärimaa, Kaisa Lehtimäki, Juha Kukkonen & Mikhail Saltychev (2017) Surgery or conservative treatment for rotator cuff tear: a meta-analysis, *Disability and Rehabilitation*, 39:14, 1357-1363. 1

⁸ Longo, U.G., Risi Ambrogioni, L., Candela, V. et al. Conservative versus surgical management for patients with rotator cuff tears: a systematic review and META-analysis. *BMC Musculoskelet Disord* 22, 50 (2021). <https://doi.org/10.1186/s12891-020-03872-4>

9. Summary of public consultation input

Consultation input was received from two (2) professional organisations, and twelve (12) individuals (all of whom were medical specialists). The 2 organisations that submitted input were:

- Private Healthcare Australia (PHA), the peak representative body for private health insurance in Australia; and
- PrecisionMed, a leading supplier of high-quality human biological material for research.

All consultation feedback received from the medical specialists (orthopaedic surgeons) was supportive of the application. Private Healthcare Australia (PHA) raised concerns with the application and did not support the proposed listing (see below). The feedback from PrecisionMed contained a quasi-registry level analysis on the cost-effective benefit value of the REGENETEN implant.

Benefits

- The implant is considered to be safe, with low probability of graft reaction, is well tolerated and is completely resorbed.
- The implant provides some structural support, aims to assist the tendon healing process, and results in improved patient outcomes, shorter recovery time and earlier return to work.
- Lowers the risk of revision surgery if the repair does not heal, and therefore more cost-effective.
- Some specialists noted that the implant had good results in patients with partial-thickness tear.
- The implant is useful for patients with partial rotator cuff tears of sufficient severity to be symptomatic, but not large enough to require a complete repair
- Improving equity of access, as currently patients who would benefit from the device do not have the financial means to access it.

Disadvantages

- Listing of this device would increase private health insurance premiums (implant costs, hospital costs and medical rebates).

Additional Comments

- Early results promising but long-term data are required.
- There are gaps in clinical evidence of reduction in revisions, biological evidence of enriched tissue strength and data to support patient satisfaction.
- Cost of the implant cited as a current barrier to access.
- Routine conservative management would include physiotherapy before and after surgery.
- The funding for pre- and post-operative physiotherapy is important.
- A high-quality study is need that is independent of consultant surgeons associated with the sponsor
- concerns that this device would be used in all parts of the body where ligaments/tendons exist.
- Empirical, quasi registry level data suggests the cost-effective PL benefit value of the REGENETEN patch, assuming it was used prophylactically is likely to be between \$0 and \$350.

10. Characteristics of the evidence base

In response to MSAC recommendations in the previous application (MSAC application 1593), the ADAR provided evidence for using bovine BCI to repair PTRCT and FTRCT based on three main randomised controlled trials (RCTs) identified through a systematic literature search, and unpublished literature made available by the manufacturer or lead investigator. The ADAR provided evidence related to PTRCT based on two RCTs (Wang et al., 2023⁹ and Camacho-Chacon et al., 2023¹⁰) and evidence related to FTRCT based on one RCT (Ruiz Ibán et al., 2023^{11, 12}). Data from Camacho-Chacon et al., 2023 were used to inform the economic evaluation for Population 1 and data from Ruiz Ibán et al., 2023 were used to inform the economic evaluation for Population 2. In addition to these RCTs, the ADAR provided safety and effectiveness evidence based on other clinical trials identified in the systematic literature search. Table 3 summarised the key features of the included evidence based on RCTs.

Table 3: Key features of the included evidence

References	N	Design/ duration	Risk of bias*	Patient population	Outcome(s)	Intervention	Comparator	Use in economic evaluation
Population 1 (PTRCT)								
Wang et al. (2023)	29	Australian, prospective, MC RCT of two-year duration.	High	High-grade (≥50%) PTRCT as noted on a 3-Tesla MRI scan	ASES score; SANE; CMS; VR-12; MRI; AEs GRC	Isolated REGENETEN implant	Repair using suture anchors	No
Camacho-Chacon et al. (2023)	60	Prospective, patient-blinded, single surgeon RCT of two-year duration.	Low	Patients presenting with a small to medium posterolateral FTRCT	ASES Score; VAS; CMS; Biopsy; MRI; Satisfaction; Work Status; AEs	Isolated REGENETEN implant	Repair using HEALICOIL REGENESOR B anchors and suture anchors	Yes
Population 2 (FTRCT)								
Ruiz Ibán et al. (2023)	120	Prospective, MC, triple blinded RCT of one year's duration.	Low	Non-acute symptomatic (>3 months) posterolateral FTRCT with anteroposterior size between 1 and 4 cm	CMS; ASES Score; EQ-5D-5L; Brief Pain Inventory; MRI – integrity of repaired tendon using the Sugaya score; AEs	Surgical procedure + augmentation with the REGENETEN Bioinductive Implant	Surgical procedure only. No augmentation with REGENETEN	Yes

Source: Table 18, pg70 of the MSAC application 1593.1 ADAR + inline commentary and Ruiz Ibán et al., 2023

Abbreviations: AEs = Adverse Events; ASES = American Shoulder and Elbow Society; CMS = Constant Murley Score; EQ-5D-5L = EuroQol-five dimension scale- 5 level; FTRCT = Full-thickness rotator cuff tear; GRC = Global Rating of Change Scale; MRI = Magnetic Resonance Imaging; MC = Multicentre; PTRCT = Partial-thickness rotator cuff tear; RCT = Randomised controlled trial; SANE = Single Assessment Numeric Evaluation score, VAS = Visual Analogue Scale; VR-12 = Veterans Rand-12.

Notes: * The risk of bias of the three RCTs was assessed by the assessment group using the Cochrane Risk of Bias tool v2.0.

⁹ Wang A. (2023). Investigator Initiated Study Clinical Report: Interim Results (ACTRN12620000926932). Smith & Nephew.

¹⁰ Camacho-Chacon J. A. (2023). Investigator Initiated Clinical Report: Final Two-Year Results (Camacho-Chacon and colleagues). Smith & Nephew.

¹¹ Ruiz Iban. (2023). Investigator Initiated Study Clinical Report: Final Results (Ruiz Iban). Smith & Nephew.

¹² Ruiz Ibán, M., García Navlet, M., Moros Marco, S., Diaz Heredia, J., Hernando Sánchez, A., Ruiz Díaz, R., Vaquero Comino, C., Rosas Ojeda, M. L., Del Monte Bello, G., & Ávila Lafuente, J. L. (2023). Augmentation of a Transosseous-Equivalent Repair in Posterolateral Nonacute Rotator Cuff Tears with a Bioinductive Collagen Implant Decreases the Retear Rate at One Year: A Randomized Controlled Trial. *Arthroscopy*. <https://doi.org/10.1016/j.arthro.2023.12.014>

Wang et al., 2023 and Ruiz Ibán et al., 2023 were sponsored by the applicant whereas Camacho-Chacon et al., 2023 was an unpublished literature made available by the lead investigator upon the applicant's request. Wang et al., 2023 was conducted in Australia whereas both Camacho-Chacon et al., 2023 and Ruiz Ibán et al., 2023 were conducted in Spain.

Participants in the Wang et al., 2023 trial had symptomatic high-grade PTRCT based on magnetic resonance imaging (MRI) scans. This trial included a higher percentage of males (57%) in the REGENETEN group compared to the control group (40%). The mean age of study participants was slightly higher in the REGENETEN group compared to the control group (57.6 years vs 56.3 years). Wang et al., 2023 only reported interim data with three months of follow up because only 29 patients were enrolled over the three-year trial period. Therefore, the evidence provided based on the Wang et al., 2023 trial was deemed to be of low certainty due to the high risk of bias including patients were not blinded for treatment allocation, small sample size and short follow up duration. Participants in Camacho-Chacon et al., 2023 trial had small-to-medium size posterosuperior FTRCT confirmed by MRI. This trial did not report any significant difference in demographic characteristics in terms of employment status, nicotine usage and diabetes or baseline tear characteristics between groups. Of note, the evidence from Camacho-Chacon et al., 2023 was based on the study clinical report (CSR) and no data were provided for the differences in certain characteristics such as age and gender between the two arms that might influence response to treatment.

Camacho-Chacon et al., 2023 was a single-surgeon, patient blinded RCT designed to evaluate tendon integrity following surgical treatment for FTRCT.⁸ However, the ADAR used Camacho-Chacon et al., 2023 trial to provide evidence related to the PTRCT. The ADAR claimed that this trial demonstrated the effectiveness of isolated bioinductive repair (IBR) intervention, which used REGENETEN without underlying suture anchors and similar to the procedure used to repair PTRCT. The ADAR justified using this trial as evidence related to PTRCT by stating that in the extreme case of a small/medium full-thickness tears, stability remains intact through the rotator cuff cable. Thus, the ADAR believed that the results were easily generalisable to the less severe, high-grade PTRCT. The commentary noted that the isolated IBR procedure used in that trial was a procedure commonly used to repair PTRCT with no sutures/suture anchors or other mechanical/structural devices, and hence the procedure outlined in the Camacho-Chacon et al., 2023 trial was in line with the procedures reported in other PTRCT studies. However, the Camacho-Chacon et al., 2023 trial included patients with supraspinatus full-thickness tear and the lesions were either small (<1cm) or medium (1-3cm) based on Cofield Classification, which was used to classify FTRCT. The Camacho-Chacon et al., 2023 trial was a single surgeon trial, and therefore, the use of PTRCT technique to repair FTRCT might not reflect actual practice in the clinical setting. Thus, the commentary considered the study population in the Camacho-Chacon et al., 2023 trial was in line with Population 2 (FTRCT) and it was therefore inappropriate to be used for Population 1 (PTRCT).

The Ruiz Ibán et al., 2023 trial included patients with FTRCT with an intraoperative anterior posterior size between 1 and 4 cm (medium to large). The commentary noted that this study population did not include patients with small (less than 1cm) and massive FTRCT lesions, which could affect its applicability to all patients under Population 2. Of note, there were no significant differences between groups at baseline in related to demographic characteristics and functional outcomes including patient reported outcomes (PROs).

Both the Camacho-Chacon et al., 2023 and Ruiz Ibán et al., 2023 studies were not conducted in the Australian setting, which could affect their applicability to the Australian practice. Evidence suggests more than 50% of those aged over 50 years have either symptomatic or asymptomatic

tears in Australia.¹³ Furthermore, 13% of all shoulder problems presented to general practitioners (GPs) are work-related and occupations which involve the use of arms repetitively resulted in higher incidence of reported rotator cuff syndrome. The incidence of rotator cuff syndrome presented to GPs was approximately 13.3 per 1000 patients per year.¹⁴ Poor prognosis is associated with increasing age, female sex, severe and recurrent symptoms at presentation. As Camacho-Chacon et al., 2023 did not report age and sex distribution of the study sample, it was not possible to comment on applicability of this trial to the Australian setting in terms of demographic characteristics. However, 63% of the participants in both groups of the Camacho-Chacon et al., 2023 trial reported type of employment as heavy work. The Ruiz Ibán et al., 2023 trial reported a mean age of 56.6 years in the REGENETEN group and 58.7 years in the control group, which was comparable to 50% of those aged over 50 years having either symptomatic or asymptomatic tears in Australia. Furthermore, 82% of the REGENETEN group and 73% of the control group were from the active labour force in the Ruiz Ibán et al., 2023 trial.

11. Comparative safety

The ADAR provided safety outcomes for both populations based on two RCTs (Ruiz Ibán et al., 2023; and Camacho-Chacon et al., 2023). The main safety outcomes presented were adhesive capsulitis, symptomatic re-tear/failure to heal, infection (deep/superficial), death, superficial skin issues (burn), mass (defined as an 8x2x4mm mass on one-year MRI) and extrusion of anchor.

The ADAR provided evidence of safety for Population 1: PTRCT based on Camacho-Chacon et al., 2023 trial. The commentary assessed the safety evidence for Population 1 was uncertain as Camacho-Chacon et al., 2023 is not relevant for Population 1. Of note, the Wang et al., 2023 trial reported no complications in either group for hospital indicators such as death, readmission, return to surgery and outlier length of stay. However, the ADAR did not include the Wang et al., 2023 trial in the comparative safety evidence because it reported only interim results. The commentary considered this to be reasonable as the interim results were based on a smaller sample size and shorter follow up duration.

For Population 2, the results from Ruiz Ibán et al., 2023 indicated that there was no significant difference in incidence of safety outcomes in the intervention and control groups. The ADAR claimed that REGENETEN was deemed to be no less safe than standard of care rotator cuff repair based on the Ruiz Ibán et al., 2023 trial in Population 2. The commentary considered this was reasonable. Of note, the previous application (MSAC application 1593) also claimed non-inferior safety based on indirect comparisons.

In addition to the evidence present in the RCTs, the ADAR provided combined incidence of adverse events for REGENETEN group only for Population 1 and Population 2 based on the Ruiz Ibán et al., 2023 RCT and BCI single arm clinical trials. The approach used to combine the incidence in single arm trials and RCT was not clear from the ADAR. Furthermore, single arm studies did not provide comparative evidence for the safety outcomes in REGENETEN and control groups. Importantly, as in the previous application (MSAC application 1593), the safety outcomes reported in the reapplication ADAR were also based on studies with a relatively short duration of follow up (less than two years). Therefore, the commentary considered the long-term safety of REGENETEN in both populations 1 and 2 was uncertain.

¹³Brun S. (2012). Shoulder injuries Management in general practice. Australian Journal for General Practitioners 41: 217-220. <https://www.racgp.org.au/afp/2012/april/shoulder-injuries>

¹⁴Hopman K, Krahe L, Luke smith S, McColl AR, & Vine K. (2013). "Clinical Practice Guidelines for the Management of Rotator Cuff Syndrome in the Workplace". The University of New South Wales. <https://rcs.med.unsw.edu.au/sites/default/files/rcs/page/RotatorCuffSyndromeGuidelines.pdf>

12. Comparative effectiveness

The ADAR provided comparative evidence based on functional outcomes including patient reported outcomes (PROs) and imaging-based outcomes. PROs were based on commonly used measures such as Western Ontario Rotator Cuff Index (WORC), American Shoulder and Elbow Society (ASES) and Single Assessment Numeric Evaluation (SANE) scores among patients with PTRCT or FTRCT.

Population 1 – PTRCT Patients (PICO set 1)

The ADAR presented two RCTS as the primary evidence of effectiveness for Population 1: Wang et al., 2023 and Camacho-Chacon et al., 2023. However, MSAC did not accept that the Camacho-Chacon et al., 2023 trial was relevant to Population 1. Table 4 summarises the comparative efficacy results based on the interim results of Wang et al., 2023 for Population 1. None of the data from Wang et al, 2023 trial were used in the economic evaluation.

Table 4: Comparative efficacy results of REGENETEN vs. SOC from Wang et al. (CSR Interim; 2023) for Population 1

	Baseline		6 weeks		3 months	
	REG N = 14	SOC N = 15	REG N = 14	SOC N = 13	REG N = 13	SOC N = 12
Functional outcomes including patient reported outcomes*						
WORC Score; mean (SD)	1,167 (283)	1,280 (296)	905 (320)	1,347 (249)	579 (428)	916 (345)
WORC Symptom; mean (SD)	49.4 (19.0)	48.5 (17.6)	24.1 (14.5)	39.6 (17.6)	20.8 (19.3)	25.4 (14.1)
WORC Lifestyle; mean (SD)	55.7 (20.0)	60.3 (25.2)	41.5 (25.3)	67.0 (24.6)	25.3 (22.5)	37.3 (22.9)
ASES; mean (SD)	53.2 (15.1)	54.2 (17.0)	67.6 (11.8)	48.0 (15.1)	79.4 (13.4)	72.2 (12.8)
SANE; mean (SD)	45.4 (19.5)	43.5 (18.4)	54.2 (20.3)	38.1 (23.1)	76.9 (19.4)	65.8 (19.9)
VR-12 PCS; mean (SD)	39.9 (10.0)	39.5 (8.2)	41.2 (10.6)	35.5 (7.6)	51.5 (9.0)	43.4 (8.7)
VR-12 MCS; mean (SD)	42.8 (9.8)	41.7 (4.6)	46.3 (8.6)	43.3 (6.8)	41.7 (6.1)	42.8 (5.8)

Source: Table 22, pg83 of the MSAC 1593.1 application ADAR + inline commentary

ASES = American Shoulder and Elbow Society; CSR = Study clinical report; MCS = Mental Component; PCS = Physical Component; REG = REGENETEN; SANE = Single Assessment Numeric Evaluation; SD = Standard deviation; SOC = Standard of Care; VR = Veterans Rand; WORC = Western Ontario Rotator Cuff Index

Notes: **Bold** indicates groups are significantly different to each other at the time period, determined by an independent t-test.

*Maximum score for the WORC is 2100 and the lower scores indicates greater function. For the ASES, SANE and VR, higher scores indicate better outcomes for patients.

Wang et al., 2023 reported that the REGENETEN group achieved a significantly lower WORC score (indicates greater function), higher SANE score at both six weeks and three months and higher ASES score at six weeks compared to the control group.

The ADAR also summarised the comparative efficacy results from the Camacho-Chacon et al., 2023 et al., trial for Population 1 (Table 5). Improvement in the ASES score from the Camacho-Chacon et al., 2023 trial were used in the economic evaluation of the Population 1.

Table 5: Comparative efficacy results of REGENETEN vs SOC from Camacho-Chacon et al., 2023 for Population 1

	Baseline		6 months		12 months		24 months	
	REG N=30	SOC N=30	REG N=30	SOC N=30	REG N=30	SOC N=30	REG N=30	SOC N=30
Functional outcomes including patient reported outcomes								
ASES score								
Median (IQR)	49.0 (4.0)	48.0 (2.0)	82.0 (5.0)	68.0 (5.0)	87.0 (5.0)	75.0 (2.0)	88.0 (5.0)	80.0 (5.0)
Percentage of patients meeting the MCID	N/A	N/A	30 (100%)	29 (96.7%)	30 (100%)	30 (100%)	30 (100%)	30 (100%)
Percentage of patients meeting the SCB	N/A	N/A	30 (100%)	26 (86.67%)	30 (100%)	30 (100%)	30 (100%)	30 (100%)
CMS score								
Median (IQR)	59.0 (2.0)	57.0 (4.0)	76.0 (4.0)	63.0 (5.0)	86.0 (5.0)	72.0 (4.0)	88.0 (2.0)	77.0 (3.0)
Percentage of patients meeting the MCID	N/A	N/A	30 (100%)	5 (16.67%)	30 (100%)	30 (100%)	30 (100%)	30 (100%)
Percentage of patients meeting the SCB	N/A	N/A	30 (100%)	20 (66.67%)	30 (100%)	30 (100%)	30 (100%)	30 (100%)
VAS	7.0 (1.0)	6.5 (1.0)	0.0 (0.0)	1.0 (1.0)	0.0 (0.0)	1.0 (1.0)	0.0 (0.0)	0.0 (0.0)
Satisfaction (Ne/S/VS)	N/A	N/A	N/A	N/A	0/3/27	2/22/6	0/3/27	0/19/11
Imaging-based outcomes								
Tendon thickness (mm) Median (IQR)	4.19 (0.03)	4.18 (0.03)	6.21 (0.32)	5.01 (0.22)	6.28 (0.29)	5.04 (0.14)	6.28 (0.25)	5.04 (0.15)

Source: Table 20, pg80-81, Table 31, pg92, Table 32, pg92, Table 33, pg93, Table 34, pg94, Table 35, pg94 of the MSAC 1593.1 application ADAR + inline commentary

Abbreviations: ASES = American Shoulder and Elbow Society; CMS = Constant-Murley Score; IQR = Inter quartile range; MCID = minimal clinically important difference; Ne = neutral; N/A = not applicable; REG = REGENETEN; S = Satisfied; SCB = substantial clinical benefit; SOC = Standard of Care; VAS = Visual Analogue Scale; VS = Very Satisfied.

Notes: **Bold** indicates significant differences between groups at each evaluation. Except for VAS, higher scores in other measures indicate better outcomes for patients.

Camacho-Chacon et al., 2023 reported a significant improvement in the ASES and the CMS scores of patients in the REGENETEN group compared to the control group at each evaluation point. The minimal clinically important difference (MCID) and substantial clinical benefit (SCB) for ASES were improvements in ASES scores of 15.5 and 17.5, respectively. The MCID and SCB for CMS were 10.4 and 5.5, respectively. Camacho-Chacon et al., 2023 reported that patients in the REGENETEN arm presented with a median of 0 pain as per the Visual Analogue Scale (VAS) - pain scale at the 6, 12 and 24-month evaluations, whereas the control group did not reach a median of 0 pain until the 24-month evaluation. Patient satisfaction scores were significantly better in the REGENETEN arm of the trial in comparison to the control group at both the 12-month and 24-month evaluations. The Camacho-Chacon et al., 2023 trial also reported a significant improvement in tendon thickness measured by post operative MRI in the REGENETEN group compared to the control group.

Secondary effectiveness outcomes: Post-Operative Return to Function and Return to Work

The Camacho-Chacon et al., 2023 trial reported significantly better post-operative return to function outcomes in the REGENETEN arm compared to the control arm (Table 6). Return to work data were used in the scenario analysis in the economic evaluation for Population 1.

Table 6: Post-Operative Return to Function and Work by Group from Camacho-Chacon et al., 2023 for Population 1

Characteristic	REGENETEN	Control	p-value
Employment status [n (%)]			0.731
Full-time	26 (86.7%)	24 (80.0%)	
Part-time	4 (13.3%)	6 (20.0%)	
Employment status change [n (%)]			0.314
No Change in Status	22 (84.6%)	17 (70.8%)	
Time to RTW number of days - median (IQR)	90.0 (25.0)	163.5 (24.0)	<0.0001
Sling Time number of days - median (IQR)	12.5 (3.00)	27.0 (3.0)	<0.0001

Source: Table 36, pg95 of the MSAC 1593.1 application ADAR + inline commentary

Abbreviations: IQR = interquartile range; RTW=return to work

Notes: Change in employment status is a comparison of pre-operative work status to post-operative works status. Numbers in **bold** indicate significant differences between groups

The commentary considered that the clinical effectiveness evidence for Population 1 was uncertain as Wang et al., 2023 provided interim results with a small sample size and short term follow-up. Moreover, the study population of Camacho-Chacon et al., 2023 is not relevant for Population 1 because this trial included patients with FTRCT.

In addition to the evidence based on Wang et al., 2023 and Camacho-Chacon et al., 2023, the ADAR provided additional evidence for reduced rehabilitation burden, time to return to work, time to return to daily activities and physiotherapy visits based on single arm studies. However, the commentary considered that this evidence was uncertain given the non-comparative nature of the single arm studies presented.

Population 2 – FTRCT Patients (PICO set 2)

The ADAR presented findings from the Ruiz Ibán et al., 2023 RCT as the primary evidence of effectiveness for Population 2 (Table 7). The imaging-based retear rates from this trial were used in the economic evaluation for Population 2.

Table 7: Comparative efficacy results of REGENETEN vs. SOC from Ruiz Ibán et al., 2023 for Population 2

	3 months		6 months		12 months	
	REG N=61	SOC N=63	REG N=61	SOC N=63	REG N=60	SOC N=62
Functional outcomes including patient reported outcomes						
Pain progression; mean (SD)	3.02 (2.0)	3.35 (2.31)	2.08 (1.97)	2.18 (2.10)	1.50 (2.07)	1.52 (2.27)
ASES; mean (SD)	53.0 (18.0)	53.9 (18.9)	71.0 (20.8)	70.8 (20.8)	78.4 (23.0)	78.7 (24.5)
CMS; mean (SD)	44.6 (16.5)	46.3 (16.0)	65.3 (18.9)	64.7 (19.0)	75.8 (20.2)	77.2 (18.5)
EQ-5D-5L (TTO)	2.1 (0.7)	2.1 (0.6)	1.8 (0.6)	1.8 (0.7)	1.6 (0.6)	1.6 (0.6)
EQ-5D-5L (VAS)	73.2 (15.2)	68.0 (17.5)	77.0 (16.9)	74.2 (17.3)	78.1 (16.5)	74.9 (20.8)
Imaging based outcomes						
Retear rates (n/N (%))	N/A	N/A	N/A	N/A	5/60 (8.3%)	16/62 (25.8%)
Tendon Thickness (mm)	N/A	N/A	N/A	N/A	Footprint:4.5 10mm medial to footprint: 4.86 20mm medial to footprint: 6.12	Footprint:3.9 10mm medial to footprint: 4.33 20mm medial to footprint:5.78

Source: Table 20, p80-81, Table 39, pg99, Figure 15, pg100, Table 41,42,43, pg103 of the MSAC 1593.1 application ADAR + inline commentary

Abbreviations: ASES = American Shoulder and Elbow Society; CMS = Constant-Murley Score; EQ-5D-5L = EuroQol-five dimension scale-five level; N/A = not applicable; REG = REGENETEN; SD = Standard deviation; SOC = Standard of Care; TTO = Time-trade off; VAS = Visual Analogue Scale.

Notes: **Bold** indicates significant differences between groups.

Ruiz Ibán et al.,2023 reported a significant improvement in PROs (pain scores, CMS, ASES score or EuroQol-five dimension scale (EQ-5D-5L)) from baseline in the intervention and control groups. However, there were no significant differences between REGENETEN and the control group in those outcomes at any timepoint. All patients improved approximately 30-points in the CMS and 24-points in the ASES score and achieved the MCID (15.5 in ASES score and 10.4 in the CMS score).

In terms of imaging based outcomes, Ruiz Ibán et al.,2023 reported a significantly lower re-tear rate (8.3 vs 25.8%; p=0.01), a three times lower risk of re-tear (Relative risk (RR)=0.32; 95% CI:0.13–0.83) and a significant increase in tendon thickness in the REGENETEN group compared to the control group at both the footprint (p=0.025) and 10mm medial to the footprint (p=0.049). The commentary noted that the improvement in the imaging-based outcomes in the REGENETEN group compared with standard of care were not correlated with an improvement in PROs.

In addition to the effectiveness evidence based on the Ruiz Ibán et al., 2023 trial, the ADAR provided evidence from single arm studies suggesting improved tendon integrity and thickness, reduced re-tear rates and improvement in QoL with REGENETEN. However, the commentary considered that with the exception of the Ferreira Barros, 2022 trial, which reported interim results, single arm studies did not provide comparative evidence for the REGENETEN and the control groups.

Clinical claim

The clinical claim is that the REGENETEN results in superior health outcomes for patients with rotator cuff tears through improved efficacy and a non-inferior safety in comparison to treatment with standard surgical repair. The clinical claim of superior effectiveness and noninferior safety

for Population 1 is uncertain because:

- Wang et al., 2023 has a high risk of bias, a small sample size (n =29) and a short-term follow-up of three months.
- The study population of Camacho-Chacon et al., 2023 is not relevant for Population 1 (PTRCT) because this trial included patients with FTRCT.

The clinical claim of superior effectiveness and noninferior safety for Population 2 is uncertain because:

- The results from the main trial, Ruiz Ibán et al., 2023, showed superiority in imaging-based outcomes such as retear rates. However, no significant differences were reported in PROs compared to standard of care (e.g., the CMS, ASES score or EQ-5D-5L).
- The noninferiority in safety is reasonable; however, the long-term outcomes of safety and effectiveness were uncertain because Ruiz Ibán et al., 2023 had only 12 months of follow-up.

13. Economic evaluation

The previous application (MSAC application 1593)¹ presented a single economic evaluation (cost-utility analysis) for both populations with a 2-year time horizon. Table 8 summarises the economic evaluations presented in the previous application and the current re-application.

Table 8: Summary of the economic evaluation presented in the previous application and the current reapplication

Component	Previous application (application 1593)	Current re-application (application 1593.1)	
	PTRCT & FTRCT	PTRCT (Population 1)	FTRCT (Population 2)
Perspective	Health care system perspective	Health care system perspective	Health care system perspective
Type(s) of analysis	CUA	CEA	CUA
Time horizon	2 years	2 years	2 years
Outcomes	Retear rate, incomplete healing rates, QALY	Change in MCID of ASES score	QALY
Methods used to generate results	Expected value analysis	Decision tree	Decision tree
Health states	PTRCT: Re-tear, successful surgery FTRCT: Incomplete healing (comprised of full re-tears and partial re-tears), successful surgery	MCID change in ASES score from baseline No MCID change in ASES score from baseline	Tear heals; Tear fails to heal; Revision surgery; Reverse total shoulder arthroplasty; Conservative management
Discount rate	5%	5%	5%
Software	Microsoft Excel	Microsoft Excel	Microsoft Excel

Source: Table 7, pg17 of the MSAC application 1593 public summary document and Table 52, pg133, Table 63, pg148 of the MSAC 1593.1 application ADAR + inline commentary.

Abbreviations: ASES = American Shoulder and Elbow Society; CEA= Cost-effectiveness analysis; CUA = Cost utility analysis; FTRCT = Full-thickness rotator cuff tear; MCID = Minimal clinically important difference; PTRCT = Partial-thickness rotator cuff tear; QALY = Quality adjusted life years.

The key assumptions in the previous ADAR model structure were proxy re-tear rates for revision surgery for both subpopulations, prevalence of PTRCTs of 71% and FTRCTs of 29% in the pooled incremental cost-effectiveness ratio (ICER) and the entire two years spent with pre-op utility for

re-tears. Overall, MSAC considered that the previous model structure was not well justified due to issues with the chosen health states and the ability to accurately reflect utility values for these health states and the relationship between revision surgery, incomplete healing and re-tear rates was not well defined or supported by the evidence (MSAC 1593 PSD, pg17-18). The re-application presented a cost-effectiveness analysis (CEA) for Population 1 (PTRCT) and a cost-utility analysis (CUA) for Population 2 (FTRCT), based on the clinical claim of superior effectiveness and non-inferior safety compared with standard surgical repair.

For Population 1 (PTRCT), the ADAR presented a CEA, with the health outcomes expressed in the change in the MCID of the ASES score. The ADAR justified this approach by claiming that the MCID is considered a suitable proxy for treatment success in PTRCT given there is no validated approach for mapping ASES scores into utility values to perform a CUA. The ASES score is an important functional outcome used to assess the clinical effectiveness of patients with symptomatic PTRCT. Therefore, the commentary considered it was reasonable to conduct a CEA in the PTRCT population. For Population 2 (FTRCT), the ADAR provided a CUA, with the health outcomes expressed in quality-adjusted life years (QALYs) gained. The commentary considered the population, outcomes and the type of economic analysis were appropriate and in line with MSAC 1593.1 Ratified PICO Confirmation. The commentary also considered the perspective and discount rate were appropriate for both subpopulations. However, the ADAR did not include continued CM as an additional comparator for the Population 1 as suggested by the PASC. Also, the commentary identified issues with the model and the model input parameters (to be discussed in detail in the relevant sections below).

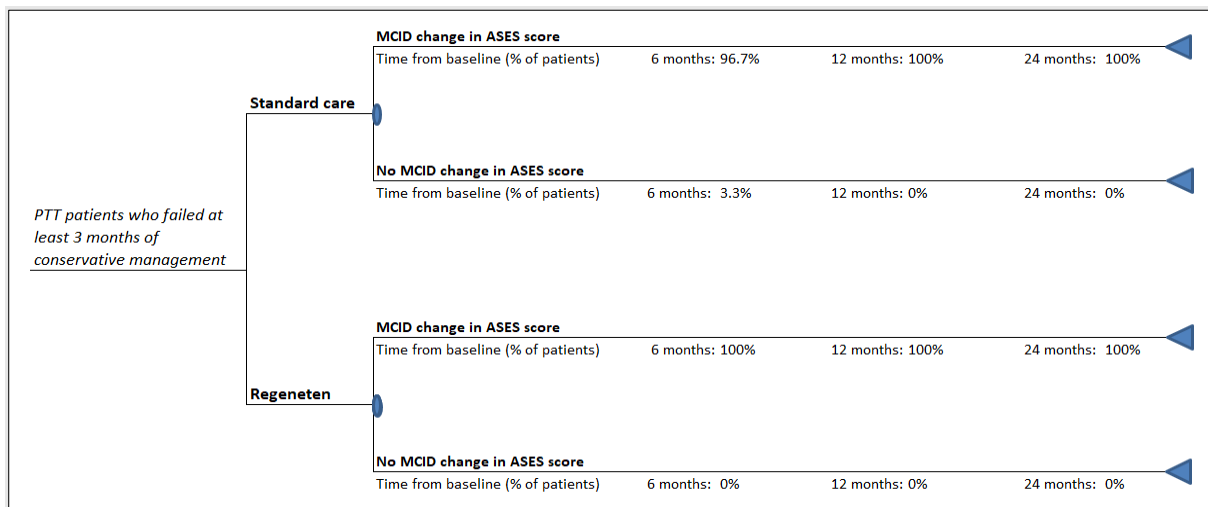
Population 1: PTRCT (PICO set 1)

Method

Model structure

The ADAR presented an economic evaluation using a decision tree model over a two-year time horizon. This was consistent with the published literature. The decision tree model included costs of treatment for an average patient and the health outcomes were based on the percentage of patients achieving MCID change in the ASES score. Therefore, the decision tree consisted of two health states: MCID change in ASES score achieved following surgery and no MCID change in ASES score. Figure 1 presented the structure of the decision tree model in Population 1: PTRCT.

Figure 1: Decision tree structure of the economic evaluation for Population 1 (PTRCT)



Source: Figure 17, pg136 of the MSAC application 1593.1 ADAR + In line commentary

Abbreviations: ASES = American Shoulder and Elbow score; MCID = Minimal clinically important difference; PTT = Partial-thickness tear; PTRCT = Partial-thickness rotator cuff tear.

Model input parameters

The ADAR sourced the following model input parameters, predominantly from Camacho-Chacon et al., 2023.

Base case:

- Percentage of patients achieving MCID change in ASES score after 6, 12 and 24 months from baseline for REGENETEN and standard of care.
- Mean change in ASES score after 6, 12 and 24 months from baseline for REGENETEN and standard of care.
- MCID of ASES score (Jones 2020).

Scenario analysis:

- Employments status.
- Time to return to work.

As mentioned earlier, Camacho-Chacon et al., 2023 was not relevant for Population 1: PTRCT.

Model transition probabilities

The percentage of patients in each of the two health states (i.e., MCID change in ASES score achieved following surgery and no MCID change in ASES score) over two years for the base case were derived from Camacho-Chacon et al., 2023. Of note, 100% of patients in both the REGENETEN and control groups achieved MCID change in the ASES score by 12 months.

Health outcomes

The ADAR used MCID change in the ASES score as the main outcome for the economic model for Population 1. The commentary considered the use of ASES reasonable as the studies recommend using ASES over other PROs such as WORC in patients undergoing rotator cuff repair due to less responder and administrative burden in ASES¹⁵. The data for MCID change in the ASES was derived from Camacho-Chacon et al., 2023, which was not relevant for Population 1. The ADAR considered that the MCID in ASES is equivalent to a score of 15.5. The MCID of 15.5 was based on systematic review¹⁶ which reported crude average of MCIDs in six included studies, hence the credibility was questionable. Of note, other studies reported different values such as 11.1^{17,18} for MCID in ASES.

Table 9 summarised the inputs used in the economic evaluation for PTRCT based on the average ASES score. The ADAR calculated average ASES score using the ASES score at the beginning and end of each period, and MCID change was calculated by dividing the average ASES score by MCID (MCID=15.5). The commentary considered that average ASES score and MCID change should be referred to as change in ASES from the previous period and number of unit changes in MCIDs, respectively. The commentary also considered that MCID represents the smallest change in an outcome that a patient would perceive as clinically meaningful, and therefore, the MCID offers a threshold to dichotomise data for the assessment of response. It was evident that 100% of the patients in the REGENETEN group and 97% of the patients in the control group achieved MCID by six months in Camacho-Chacon et al., 2023. Thus, the commentary considered it was

¹⁵ Baumgarten KM, Barthman BJ, Chang PS. The American Shoulder and Elbow Score Is Highly Correlated with the Western Ontario Rotator Cuff Index and Has Less Responder and Administrator Burden. *Arthrosc Sports Med Rehabil*. 2021 Sep 21;3(6):e1637-e1643

¹⁶ Jones, I. A., R. Togashi, N. Heckmann and C. T. Vangsness, Jr. (2020). "Minimal clinically important difference (MCID) for patient-reported shoulder outcomes." *J Shoulder Elbow Surg* 29(7): 1484-1492.

¹⁷ Bushnell, B. D., P. M. Connor, H. W. Harris, C. P. Ho, S. W. Trenhaile and J. S. Abrams (2022). "Two-year outcomes with a bioinductive collagen implant used in augmentation of arthroscopic repair of full-thickness rotator cuff tears: final results of a prospective multicenter study." *J Shoulder Elbow Surg* 31(12): 2532-2541.

¹⁸ Cvetanovich, G. L., A. K. Gowd, J. N. Liu, B. U. Nwachukwu, B. C. Cabarcas, B. J. Cole, B. Forsythe, A. A. Romeo and N. N. Verma (2019). "Establishing clinically significant outcome after arthroscopic rotator cuff repair." *Journal of Shoulder and Elbow Surgery* 28(5): 939-948.

inappropriate to calculate the number of MCIDs achieved.

Camacho-Chacon et al., 2023 CSR reported only median and inter-quartile range (IQR) of ASES scores between REGENETEN and the control group over time (Table 5). Of note, the median values indicated that there was a higher improvement from baseline to six months followed by six months to 12 months in both the REGENETEN and control groups. Furthermore, median and IQR indicated that there was a very slight improvement in ASES from 12 months to 24 months in REGENETEN group. The commentary initially did not consider the average ASES score improvement reported in the economic evaluation for Population 1 (Table 56, pg140 of ADAR + in-line commentary) in the ADAR consistent with the ASES scores reported in Camacho-Chacon et al., 2023. Table 9 presents further details of ADAR’s calculations as explained in the applicant’s Pre-ESC Response.

Table 9 ADAR’s calculation of units of MCID of ASES score by treatment group - Population 1 (PTRCT)

Parameters	Standard surgical repair with REGENETEN	Standard surgical repair without REGENETEN
Step 1: ASES score from Camacho-Chacon et al., 2023 trial		
Baseline [A]	49	48
6 months [B]	82	68
12 months [C]	87	75
24 months [D]	88	80
Step 2: ASES gain for each period from baseline		
Baseline [E = A]	0	0
6 months [F = B – A]	33	20
12 months [G = C – A]	38	27
24 months [H = D – A]	39	32
Step 3: Average ASES gain considering the ASES score in the beginning and end of each period		
Baseline to 6 months [I = average(E,F)]	16.5	10.0
6 to 12 months [J = average(F,G)]	35.5	23.5
12 to 24 months [K = average(G,H) x (1-discount rate)]	36.6	28.0
Step 4: Transforming ASES gain into MCID (1 MCID = 15.5 points in ASES = L)		
Baseline to 6 months [M = I ÷ L]	1.06	0.65
6 to 12 months [N = J ÷ L]	2.29	1.52
12 to 24 months [O = K ÷ L]	2.36	1.81
Percentage of patients achieving MCID change in ASES score from Camacho-Chacon et al., 2023 trial		
Baseline to 6 months [P]	100%	96.7%
6 to 12 months [Q]	100%	100%
12 to 24 months [R]	100%	100%
Total units of MCID of ASES score weighted for period [S = (MxPx6 + NxQx6 + OXRx12) ÷ 24]	2.02	1.44

Source: Table 59, pg144 of the MSAC application 1593.1 ADAR + In line commentary; Table 1, pg6 of applicant’s Pre-ESC Response; Tab “5. PTT_Calculations” in Excel workbook titled “Economic Evaluation_REGENETEN” supplied with the ADAR. Abbreviations: ADAR = Applicant Developed Assessment Report; ASES = American Shoulder and Elbow Society; MCID = Minimal clinically important difference.

Table 10 presents the commentary’s calculations performed during the evaluation for the change in ASES from the previous period, based on the ASES scores in Table 5.

Table 10 Commentary's respecified base case analysis - Population 1 (PTRCT)

Parameters	Standard surgical repair with REGENETEN	Standard surgical repair without REGENETEN
Step 1: ASES score from Camacho-Chacon et al., 2023 trial (same as ADAR)		
Baseline [A]	49	48
6 months [B]	82	68
12 months [C]	87	75
24 months [D]	88	80
Step 2: Change in ASES from the previous period		
6 months [F = B – A]	33.0	20.0
12 months [G = C – A]	5.0	7.0
24 months [H = D – A] x (1-discount rate)]	1.0	4.8
Step 3: Number of unit change of MCID [1 MCID = 15.5 points in ASES = L]		
Baseline to 6 months [M = F ÷ L]	2.13	1.29
6 to 12 months [N = G ÷ L]	0.32	0.45
12 to 24 months [O = H ÷ L]	0.06	0.31
Percentage of patients achieving MCID change in ASES score from Camacho-Chacon et al., 2023 trial (same as ADAR)		
Baseline to 6 months [P]	100%	96.7%
6 to 12 months [Q]	100%	100%
12 to 24 months [R]	100%	100%
Commentary: Total units of MCID of ASES score weighted for period [S = (MxPx6 + NxQx6 + OxDx12) ÷ 24]	0.64	0.58
ESC corrected [T = M + N + O]	2.51	2.05

Source: Commentary Table 3 and Table 59, pp141 and 144 of the MSAC application 1593.1 ADAR + In line commentary; Table 1, pg6 of applicant's Pre-ESC Response; Tab "5. PTT_Calculations" in Excel workbook titled "Economic Evaluation_REGENETEN" supplied with the ADAR.

Abbreviations: ADAR = Applicant Developed Assessment Report; ASES = American Shoulder and Elbow Society; MCID = Minimal clinically important difference.

Health care resource use and costs

The ADAR included relevant device and material costs in both intervention and comparator arms and the commentary considered these costs appropriate. However, cost inputs needed to be updated based most recent fee updates. The ADAR did not include costs based on surgical time as REGENETEN was not expected to increase surgical time for Population 1. The ADAR also assumed that the costs associated with operating theatre and with rehabilitation following the surgical procedure were the same between REGENETEN and standard of care. Hence, these costs were not included in the model, which was reasonable.

Results of the economic evaluation

Base case

The ADAR presented a trial-based analysis for a two-year time horizon to obtain the base case results. Table 11 presents the results in the base case.

Table 11: Population 1 (PTRCT): base-case results

	Outcome measure	Standard surgical repair with REGENETEN	Standard surgical repair without REGENETEN	Difference	ICER (per additional unit of MCID of ASES score)
Base case	Costs with surgical devices	\$redacted	\$2,136	\$redacted [A]	–
ADAR's base case	Total units of MCID of ASES score weighted for period (Table 9)	2.019	1.439	0.580 [B]	\$redacted [A/B]
Commentary alternative base case analysis	Total units of MCID of ASES score weighted for period (Table 10)	0.644	0.578	0.065 [C]	\$redacted [A/C]
ESC	<i>Using Commentary's approach but correcting an error (Table 10)</i>	2.513	2.048	0.465 [E]	\$redacted [A/E]

Source: Tables 58, and Commentary Table 4, pp144-145 of MSAC application 1593.1 ADAR + In line commentary; Table 2, pg6 of applicant's Pre-ESC Response; ESC calculations.

Abbreviations: ADAR = Applicant-Developed Assessment Report; ASES = American Shoulder and Elbow Society; ESC = Evaluation Subcommittee; MCID = Minimal clinically important difference; PTRCT = Partial-thickness rotator cuff tear.

The ADAR reported that using standard surgical repair with REGENETEN in patients with symptomatic PTRCT who have failed at least three months of CM would result in an incremental benefit of 0.58 unit of MCID of ASES gained over a 2-year period when compared to standard surgical repair without REGENETEN, resulting in an ICER of \$redacted per MCID of ASES (15.5 points in the ASES score) gained. That is, treatment with REGENETEN would generate an additional treatment success (defined as a patient achieving the MCID in the ASES score) for \$redacted.

The commentary noted that the results of the ADAR's base case analysis were highly uncertain because the Camacho-Chacon et al., 2023 trial included entirely FTRCT patients and was therefore not relevant for Population 1. In addition, the commentary considered the ADAR inaccurately calculated the change in ASES score and inappropriately used the number of unit changes in MCID of ASES as the outcome of the cost-effectiveness analysis. Nevertheless, using the same approach in the ADAR, but an alternative method of calculation of change in MCID of ASES scores during the evaluation based on the ASES scores provided in Table 5, the incremental benefit of standard surgical repair with REGENETEN decreased to 0.065 unit of MCID of ASES gained over a 2-year period when compared to standard surgical repair without REGENETEN, and the resultant ICER increased to \$redacted per MCID gained.

ESC considered the commentary's approach reasonable but agreed with the Pre-ESC Response regarding an error in the last step and considered that the commentary should have added the gains in MCID for each period to get the total gain for the entire period of 24 months. The Pre-ESC Response reported that the incremental benefit should therefore be 0.50 per MCID of ASES score, resulting in an ICER of \$redacted per MCID. ESC considered that using the commentary's approach but correcting the error in the last step resulted in an incremental benefit of 0.465 and an ICER of \$redacted per unit MCID of ASES gained (Table 11).

Scenario analyses

The ADAR presented two scenario analyses for the Population 1:

- Scenario analysis based on societal perspective:

The ADAR presented a scenario analysis in societal perspective by including productivity costs. These costs were estimated using the time return to work for REGENETEN and standard of care, the percentage of each population that would be employed based on the Camacho-Chacon et al., 2023 trial and the weekly wage in Australia. The REGENETEN arm dominated in the ICER based on societal perspective.

- Scenario analysis based on SCB:

A scenario analysis presented using the SCB in the ASES score (change in ASES score of 17.5 was considered as achieving SCB) for Population 1. The ADAR claimed that the SCB is the larger change in an outcome measure that represents a more significant improvement in the patient’s condition. The ICER increased from \$redacted to \$redacted per SCB gained in the scenario analysis. The commentary noted that the results of the scenario analyses were highly uncertain as Camacho-Chacon et al., 2023 was not relevant for the Population 1 as well as the effectiveness measure calculations (i.e., change in ASES from the previous period) included in the model were not accurate.

Sensitivity analyses

The ADAR presented univariate sensitivity analyses for key inputs to the economic model for Population 1 (PTRCT). The input with the biggest impact on the ICER was MCID value for ASES score, REGENETEN kit price, followed by the cost of standard of care. Table 12 summarised the key drivers of the model.

Table 12: Key drivers of the model (Population 1: PTRCT)

Parameter	Description	Impact Base case: \$redacted /unit of MCID gained	Impact ESC (using commentary’s re-specified base case and correcting an error: \$redacted /unit of MCID gained)
Cost of intervention for Standard of care	Increase by 20% (BC = \$redacted)	High, favoured REGENETEN Use of 20% high value for the cost of standard care reduced the ICER to \$redacted /unit of MCID gained.	High, favoured REGENETEN Use of 20% high value for the cost of standard care reduced the ICER to \$redacted /unit of MCID gained.
Cost of REGENETEN Kit	Increase by 20% (BC = \$redacted)	High, favoured standard care Use of 20% high value for the cost of REGENETEN kit increased the ICER to \$redacted /MCID gained.	High, favoured standard care Use of 20% high value for the cost of REGENETEN kit increased the ICER to \$redacted /unit of MCID gained.
MCID value for ASES score	Use maximal MCID value (21.9) reported in the 6 included studies in Jones et al., 2020 review (BC = 15.5)	High, favoured REGENETEN ICER increased to \$redacted /unit of MCID gained.	High, favoured REGENETEN ICER increased to \$redacted /unit of MCID gained.

Source: Adapted from Table 62, pg144 of the MSAC application 1593.1 ADAR + In line commentary

Abbreviations: ASES = American Shoulder and Elbow Society; BC = base case; ICER = incremental cost-effectiveness ratio; MCID = Minimal clinically important difference

The results of key univariate sensitivity analyses were summarised in Table 13.

Table 13: Sensitivity analyses for Population 1 (PTRCT)

Analyses		Incremental cost	Incremental outcomes	ICER per unit change of MCIDs
Base case		redacted	0.58	redacted
Sensitivity analyses presented in the ADAR				
Discount rate for both costs and outcomes (base case: 5%)	3.5%	redacted	0.58	redacted
	0%	redacted	0.59	redacted
Cost of intervention for Standard of care (base case: \$2,136)	20% increase: \$2,563	redacted	0.58	redacted
	20% reduction: \$1,709	redacted	0.58	redacted
Cost of REGENETEN Kit (base case: \$ redacted)	20% increase: \$ redacted	redacted	0.58	redacted
	20% reduction: \$ redacted	redacted	0.58	redacted
Additional sensitivity analyses conducted during the evaluation				
Using base case analysis provided in the ADAR				
MCID for ASES score = 6.4 (minimal value of the six included studies in the Jones et al., 2020 systematic review) (base case = 15.5)		redacted	1.40	redacted
MCID for ASES score = 21.9 (maximal value of the six included studies in the Jones et al., 2020 systematic review) (base case = 15.5)		redacted	0.41	redacted
Using alternative base case analysis in commentary				
Alternative base case analysis in commentary		redacted	0.07	redacted
<i>ESC recalculation</i>		redacted	0.46	redacted
MCID for ASES score = 6.4 (minimal value of the six included studies in the Jones et al., 2020 systematic review) (base case = 15.5)		redacted	0.16	redacted
<i>ESC recalculation</i>		redacted	1.13	redacted
MCID for ASES score = 21.9 (maximal value of the six included studies in the Jones et al., 2020 systematic review) (base case = 15.5)		redacted	0.05	redacted
<i>ESC recalculation</i>		redacted	0.33	redacted
Applying lower range of the ASES score for each time period based on IQR to calculate total units of MCID of ASES score weighted for period*		redacted	0.1	redacted
<i>ESC recalculation</i>		redacted	0.59	redacted
Applying upper range of the ASES score for each time period based on IQR to calculate total units of MCID of ASES score weighted for period*		redacted	-0.01	redacted
<i>ESC recalculation</i>		redacted	0.48	redacted

Source: Adapted from Table 31, pg92 and Table 62, pg147 of the MSAC application 1593.1 ADAR + In line commentary
Abbreviations: ASES = American Shoulder and Elbow Society ICER = Incremental cost effectiveness ratio; MCID = Minimal clinically important difference; PTRCT = Partial-thickness rotator cuff tear.

Notes: *Lower and upper range of the ASES scores were retrieved from the Table 31, pg91 and Figure 12, pg91 of the MSAC application 1593.1 ADAR + In line commentary and Figure 1 of the Camacho-Chacon et al., 2023 trial CSR. Same approach used in the ADAR were used to calculate the average ASES score for each period and units of MCID of ASES score for each period. The lower range of ASES scores were 47,78,86 and 87 for REGENETEN arm and 47,67,73 and 78 for control arm in baseline, 6months, 12 months and 24 months respectively. Upper range of ASES scores were 51,84,92 and 92 for REGENETEN arm and 49,72,75 and 83 for control arm in baseline, 6months, 12 months and 24 months respectively.

Population 2: FTRCT (PICO set 2)

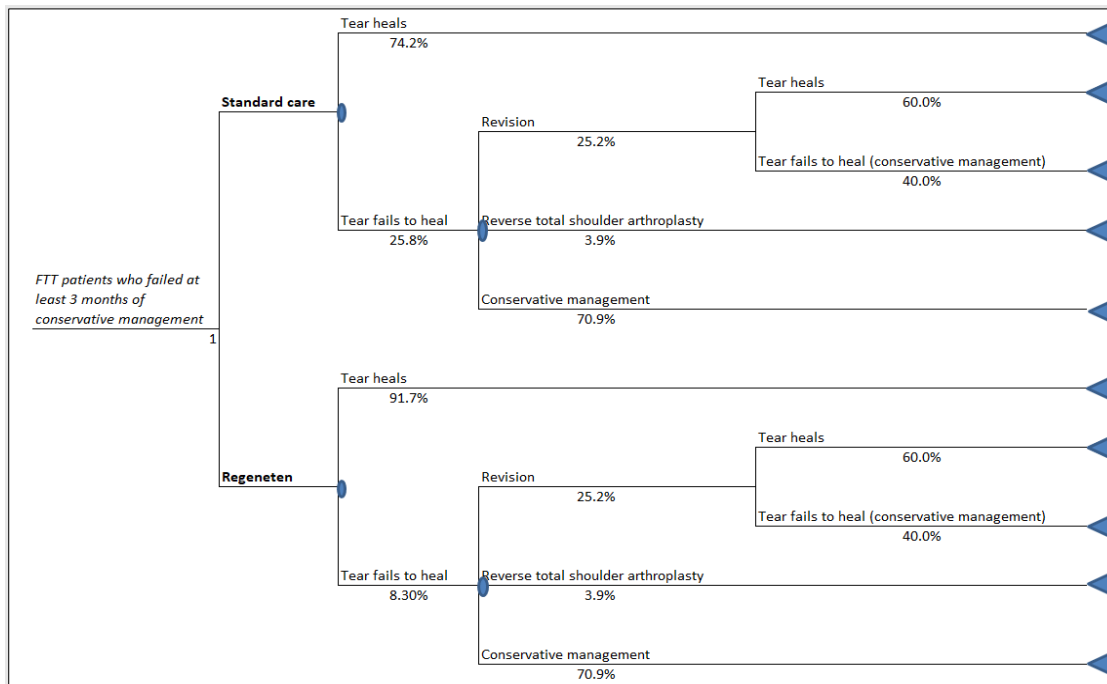
Method

Model structure

The ADAR presented an economic evaluation using a decision tree model over a two-year time horizon. The ADAR conducted a CUA by incorporating retear rates reported from the clinical literature and applying utility values to successfully treated patients and those who experienced retears. The ADAR claimed that the two-year time horizon was adopted to capture the majority of retears and any associated treatment costs.

The model structure was based on McIntyre et al., 2023¹⁹ (applicant sponsored) which evaluated the cost-effectiveness of resorbable REGENETEN in addition to conventional rotator cuff repair (RCR), compared to RCR alone, in the treatment of FTRCT over a one-year time horizon. McIntyre et al., 2023 sourced retear rates for intervention and comparator from different studies (naïve indirect comparison) and estimated an ICER of \$13,061 per healed rotator cuff tears REGENETEN compared to conventional RCR alone. Figure 2 provided the structure of the decision tree for the economic evaluation in Population 2. The decision tree model was in line with the economic model presented in McIntyre et al., 2023, except for the retear rates after revision surgery.

Figure 2: Decision tree structure of the economic evaluation for Population 2 (FTRCT)



Source: Figure 18, p151 of the MSAC application 1593.1 ADAR + In line commentary

Abbreviations: ASES = American Shoulder and Elbow score; FTRCT = Full-thickness rotator cuff tear; FTT = Full-thickness tear; MCID = Minimal clinically important difference

¹⁹ McIntyre, L. F., L. M. Nherera and T. F. Schlegel (2023). "Resorbable Bioinductive Collagen Implant Is Cost Effective in the Treatment of Rotator Cuff Tears." *Arthrosc Sports Med Rehabil* 5(2): e367-e374.

Model input parameters

The ADAR sourced the following model input parameters from Ruiz Ibán et al., 2023:

Base case analysis

- Retear rates (transition probabilities to the health states, “tear fails to heal” and “tear heal”)

Scenario analysis

- Employment status

The commentary considered the patients in this trial representative of the intended indication in Population 2, hence it was relevant for Population 2 (FTRCT).

Model transition probabilities, variables and extrapolation

The ADAR used the retear rates from Ruiz Ibán et al., 2023 for REGENETEN and standard of care after one year of follow-up to estimate the percentage of patients with tears that fail to heal for the two health states i.e., tear heals, and tear fails to heal following the surgical procedure. The ADAR did not extrapolate the retear rates from the Ruiz Ibán et al., 2023 from one to two years but assumed that the retear rates with REGENETEN and standard of care did not increase between one year and two years - total time horizon of the economic evaluation. The ADAR claimed that this is in line with the literature.¹⁵ Since Ruiz Ibán et al., 2023 did not present mean time to retear, the ADAR used an average time to retear of 6 months in the model based on an assumption related to double-row repair technique in the Bushnell et al., 2022¹⁵ study, in which patients presented with a retear in the middle of their follow-up period. Bushnell et al., 2022 was a multicentre cohort study that provided two-year outcomes of a BCI used in the repair of FTRCT. The commentary noted that the sources of average time to retear of 6 months was not clear from Bushnell et al., 2022 study.

One of the concerns raised by MSAC in the previous application was that the imaging results were problematic due to the lack of definitions for “retear,” “incomplete healing” and “treatment failure.”¹ However, the ADAR assumed that “tear fail to heal” was equivalent to the “retear rate” reported in the Ruiz Ibán et al., 2023 trial. The ADAR did not provide clear definitions of those outcomes to justify that assumption. Notably, the same approach was used in the McIntyre et al., 2023 study.

Following a retear, patients can undergo revision RCR, reverse shoulder arthroplasty, or receive CM. Data on the distribution of patients receiving one of these treatments is not available for the Australian population. Therefore, the ADAR sourced the probability of having revision RCR or reverse shoulder arthroplasty from the study by Parikh et al., 2021.²⁰ This study used the IBM Watson Health Market Scan Commercial database, which found that 25.22% and 3.9% would have debridement surgery and subacromial decompression among patient with RCR and arthroplasty respectively. ADAR approximate these values for revision surgery (reoperation surgery on index shoulder) or reverse shoulder arthroplasty, respectively. It was then assumed that the remainder (70.9%) of the patients would be managed using conservative methods. Parikh et al., 2021 reported direct and indirect economic burden associated with rotator cuff tears and repairs in the USA and the data included in the ADAR as transition probabilities were based on the treatment characteristics during the 12-month post-index period of FTRCT patients. These data were not confined to patients who had undergone revision surgery. Hence, the commentary considered that these transition probabilities were not appropriate to use in the

²⁰ Parikh, N., D. J. Martinez, I. Winer, L. Costa, D. Dua and P. Trueman (2021). "Direct and indirect economic burden associated with rotator cuff tears and repairs in the US." *Curr Med Res Opin* 37(7): 1199-1211.

economic model.

Health Outcomes

The ADAR claimed that the literature search did not identify any published CUAs with utility data for health states relevant to FTRCT in the Australian population. Therefore, the ADAR used the utilities reported in Grobet et al., 2020²¹ to inform the utility values for the health states: tear heals (0.891 and 0.950 in Year 1 and 2, respectively) and CM (0.71) after tear fails to heal post-repair.

The commentary noted that the Grobet et al., 2020 study was not confined to the patients with FTRCT. Also, the utilities reported in this study was not related to 'tear heals' or 'tear fail to heal', but utility at different time points for patients who underwent arthroscopic surgery. Therefore, approximation of first year utility and second year utility from Grobet et al., 2020 study to the utility values for 'tear heal' and 'tear fail to heal' in the economic model resulted higher utility for the 'tear fails to heal' than the 'tear heals' as well as higher than the population norm for the Australian general population,²² which is not accurate.

Furthermore, based on the Grobet et al., 2020 study, the ADAR used a utility score of 0.7 for CM and assumed that this value would remain unchanged over two years. Of note, the 0.7 utility score reported in the Grobet et al., 2020 study referred to the utility value for preoperative patients, which proxied for the utility for CM that patients would maintain throughout the entire follow-up period if they had not undergone surgery.

Importantly, the commentary noted that the ADAR did not use health related QoL data collected alongside the Ruiz Ibán et al., 2023 trial in the economic evaluation. If the ADAR used an approach based on data collected alongside the clinical trial for the economic evaluation as they approximate the utility values at different time points to tear heals and tear fail to heal based on Grobet et al., 2020 study, the ICER could be much higher than in the current model (Please see sensitivity analysis for Population 2 for more details). Of note, there was no significant difference in the EQ-5D-5L scores between the two arms of Ruiz Ibán et al., 2023.

Furthermore, the ADAR also used the Grobet et al., 2020 study to assume utility values for revision surgery or reverse arthroplasty following tear fails to heal. The ADAR assumed a utility value of 0.736 for both states (80% of the average of first year utility 0.891 and second-year utility 0.950 reported in Grobet et al., 2020 study). The ADAR claimed that a similar approach was taken by Dornan et al., 2017²³, where the authors assumed that the utility value for successful revision of arthroscopic rotator cuff repair would be 70% of the utility value for successful primary surgery. As discussed earlier, the utilities reported in Grobet et al., 2020 study were not related to utility value for successful primary surgery, but utility values at different time points. Therefore, utility value for revision surgery and reverse arthroplasty after tear fails to heal were not accurate (i.e., based on assumption and non-related values).

Health care resource use and costs

The ADAR included relevant device and material costs in both intervention and comparator arms and the commentary considered these costs appropriate. However, cost inputs needed to be updated based most recent fee updates. The ADAR did not include cost for the standard suture

²¹ Grobet, C., L. Audige, K. Eichler, F. Meier, B. Brunner, S. Wieser and M. Flury (2020). "Cost-Utility Analysis of Arthroscopic Rotator Cuff Repair: A Prospective Health Economic Study Using Real-World Data." *Arthrosc Sports Med Rehabil* 2(3): e193-e205.

²² Redwood L, Currow D, Kochovska S, Thomas SJ. Australian population norms for health-related quality of life measured using the EQ-5D-5L, and relationships with sociodemographic characteristics. *Qual Life Res.* 2024 Mar;33(3):721-733

²³ Dornan, G. J., J. C. Katthagen, D. S. Tahal, M. Petri, J. A. Greenspoon, P. J. Denard, S. S. Burkhart and P. J. Millett (2017). "Cost-Effectiveness of Arthroscopic Rotator Cuff Repair Versus Reverse Total Shoulder Arthroplasty for the Treatment of Massive Rotator Cuff Tears in Patients with Pseudoparalysis and Nonarthritic Shoulders." *Arthroscopy* 33(4): 716-725.

anchor repair in either arm as the use of REGENETEN was additional to the standard suture anchor repair in the FTRCT population. The main costs for the FTRCT population were associated with the management of patients following a retear. Patients could undergo a rotator cuff tear revision or reverse total shoulder replacement (RTSP), or stay in CM (e.g., physiotherapy session, pain medication, etc.). The ADAR sourced these cost data from different sources.

In addition to the cost estimated by MSAC for CM, the ADAR claimed that 12 physiotherapy sessions and 6 corticosteroid injections per year were added to CM in both arms as reported by Cederqvist et al., 2021.²⁴ Adding the similar number of physiotherapy sessions and corticosteroid injections for both arms overestimates the cost in the control arm given that a higher percentage of tear fails to heal in the control arm compared to the REGENETEN arm and the higher cost of physiotherapy sessions compared to corticosteroid injections.

Results of the economic evaluation

Base case

Table 14 summarised the disaggregated and aggregated costs and outcomes over two years.

Table 14: Disaggregated and aggregated costs and benefits for Population 2 (FTRCT): base-case results

Health State	REGENETEN	Standard surgery	Incremental
Average cost per patient over 2 years			
Intervention cost	redacted	-	redacted
Tear heals	-	-	-
Tear fails to heal -> Revision surgery -> Tear heals	\$149	\$465	-\$315
Tear fails to heal -> Revision surgery -> Tear fails to heal	\$132	\$410	-\$278
Tear fails to heal -> Reverse total shoulder arthroplasty	\$92	\$286	-\$194
Tear fails to heal -> Conservative Management	\$367	\$1,140	-\$773
Total average cost per patient	redacted	\$2,301	redacted
Average QALYs per patient over 2 years			
Tear heals	1.645	1.331	0.314
Tear fails to heal -> Revision surgery -> Tear heals	0.018	0.056	-0.038
Tear fails to heal -> Revision surgery -> Tear fails to heal	0.012	0.036	-0.024
Tear fails to heal -> Reverse total shoulder arthroplasty	0.005	0.014	-0.010
Tear fails to heal -> Conservative Management	0.081	0.253	-0.172
Total average QALYs per patient	1.760	1.690	0.070
Patient distribution per health state			
Tear heals	91.7%	74.2%	17.5%
Tear fails to heal -> Revision surgery -> Tear heals	1.3%	3.9%	-2.6%
Tear fails to heal -> Revision surgery -> Tear fails to heal	0.8%	2.6%	-1.8%
Tear fails to heal -> Reverse total shoulder arthroplasty	0.3%	1.0%	-0.7%
Tear fails to heal -> Conservative Management	5.9%	18.3%	-12.4%
Total	100%	100%	-

Source: Table 71, pg163 of the of the MSAC application 1593.1 ADAR + In line commentary

Abbreviations: FTRCT = full-thickness rotator cuff tear; QALY = Quality-adjusted life years

Notes: Cost and QALYs for patients in each arm were calculated based on the patient distribution per health state and relevant cost and outcomes were based on the sources described under the health outcomes and health care resource use and costs for Population 2.

²⁴ Cederqvist S, Flinkkilä T, Sormaala M, et al Non-surgical and surgical treatments for rotator cuff disease: a pragmatic randomised clinical trial with 2-year follow-up after initial rehabilitation. *Annals of the Rheumatic Diseases* 2021;80:796-802.

The incremental health outcomes with REGENETEN were derived from the higher percentage of patients in the tear heals state (due to lower retear rate). In terms of costs, REGENETEN presents a higher cost with the surgical intervention (REGENETEN kit), but a lower average cost with revision, reverse total shoulder arthroplasty and conservative management. In total, REGENETEN is associated with an incremental cost of **redacted** over two years.

Summary of base-case results

From the Australian healthcare perspective, using REGENETEN in patients with symptomatic FTRCT, the ADAR estimated that REGENETEN had an ICER of **redacted** per QALY gained. Table 15 summarised the overall results of the base case for the Population 2 (FTRCT).

Table 15: Base-case results of the model for Population 2 (FTRCT)

Parameter	REGENETEN	Standard of care	Increment
Costs	redacted	\$2,301	redacted
QALYS	1.76	1.69	0.07
Incremental cost per QALY gained			redacted

Source: Table 70, pg162 of the MSAC application 1593.1 ADAR + In line commentary
 Abbreviations: FTRCT = full-thickness rotator cuff tear; QALY = Quality-adjusted life years

The commentary noted that the results of the base case analysis were uncertain given the uncertainty in key model parameters as discussed above including health state utilities and transition probabilities.

Scenario analysis

The ADAR presented a scenario analysis based on a societal perspective by including productivity costs. These costs were estimated using the time for return to work for REGENETEN and standard of care based on McIntyre et al., 2021²⁵, the weekly wage in Australia and the percentage of each population that would be employed. The ICER was reduced to **redacted** per QALY gained.

The commentary noted that the results of the scenario analysis were uncertain as the model input parameters (e.g., health state utilities, transition probabilities) were not relevant for Population 2 as well as not accurate.

Sensitivity analyses

The ADAR presented univariate sensitivity analysis for key inputs to the model for Population 2 (FTRCT). The commentary considered that the transition probabilities of health state: tear fails to heal (REGENETEN) and tear fails to heal (Standard of care), utility value of CM after tear fails to heal and the cost of REGENETEN kit were the key drivers of the model. Table 16 summarised the key drivers of the model.

²⁵ McIntyre LF, McMillan S, Trenhaile SW, Bishai SK, Bushnell BD. Full-Thickness Rotator Cuff Tears Can Be Safely Treated With a Resorbable Bioinductive Bovine Collagen Implant: One-Year Results of a Prospective, Multicenter Registry. *Arthroscopy, Sports Medicine, and Rehabilitation*. 2021;3(5):e1473-9

Table 16: Key drivers of the model for Population 2: FTRCT

Description	Method/Value	Impact Base case: redacted /QALY gained
Probability of tear fails to heal (REGENETEN)	Percentage of patients with tear fails to heal in REGENETEN group was based on mean retear rates (CI) 3.6% - 18.1%	High, favours standard care Use of 18.1% higher value for the REGENETEN increases the ICER to redacted /QALY gained Use of
Probability of tear fails to heal (Standard of care)	Percentage of patients with tear fails to heal in standard care group was based on retear rates CI (16.6% - 37.9%)	high, favours REGENETEN Use of 16.6% lower value for the standard care increases the ICER to redacted /QALY gained
Utility value of conservative management after tear fails to heal	Utility value of conservative management was based on preoperative utility value for FTRCT patients (0.71)	High, favours REGENETEN Use of 10% higher value (0.781) for the standard care increases the ICER redacted /QALY gained.
Cost of REGENETEN kit	Cost of REGENETEN kit was based on fee allocated by the Applicant for the kit	High, favours standard care Use of 20% high value for the REGENETEN kit increase the ICER redacted /QALY gained

Source: Table 73, pg165-166 of the MSAC application 1593.1 ADAR + In line commentary

Abbreviations: FTRCT = full-thickness rotator cuff tear; ICER = Incremental cost effectiveness ratio; QALY = Quality-adjusted life years

The results of key univariate sensitivity analyses were summarised in Table 17.

During the evaluation, an additional sensitivity analysis was conducted to assess the impact of using utility values from the Ruiz Ibán et al., 2023 trial reported in Table 7. The same approach was used as in the ADAR to assess the impact, acknowledging that the data reported in the Ruiz Ibán et al, 2023 trial was for EQ-5D VAS values and approximation of utility values at different time points to utility values for tear heal and tear fail to heal health states was not accurate. The additional sensitivity analysis included values from the REGENETEN arm in Ruiz Ibán et al., 2023 for both arms as in ADAR and a utility value of 0.68 for CM after incomplete healing, and 0.78 utility of first year follow up for successful surgery (first year) was assumed. Further, a utility value of 0.80 for successful surgery (second year) was included by assuming linear increase and extrapolating the utility from Year 1 the Ruiz Ibán et al, 2023 trial to a second year. Applying the utility values from the Ruiz Ibán study increased the ICER to redacted. ESC considered the assumption that the utility of patients with incomplete healing and then successful revision surgery would be lower than CM was clinically implausible. ESC considered the estimates in the ADAR to be an appropriate proxy and did not support the utility values used to conduct the additional sensitivity analyses.

Table 17: Sensitivity analyses for Population 2: FTRCT

Analyses	Incremental cost	Incremental outcomes	ICER per QALY
Base case	redacted	0.07	redacted
Discount rate (base case: 5% for both costs and outcomes)			
3.5%	redacted	0.07	redacted
0%	redacted	0.07	redacted
Health state: tear fails to heal (REGENETEN) (base case: 8.3%)			
Lower 95% CI: 3.6%	redacted	0.09	redacted
Upper 95% CI: 18.1%	redacted	0.03	redacted
Health state: tear fails to heal (Standard of care) (base case: 25.8%)			
Lower 95% CI: 16.6%	redacted	0.03	redacted
Upper 95% CI: 37.9%	redacted	0.12	redacted
Utility value of conservative management after tear fails to heal (base case:0.710)			
10% reduction: 0.639	redacted	0.09	redacted
10% increase: 0.781	redacted	0.05	redacted
Cost of REGENETEN kit (base case: redacted)			
20% increase: redacted	redacted	0.07	redacted
20% reduction: redacted	redacted	0.07	redacted
Additional sensitivity analyses conducted during the evaluation			
Applying utility values from Ruiz Ibán et al., 2023 trial for the conservative management (0.68), successful surgery first year 0.78 and second year 0.80 *	redacted	0.04	redacted

Source: Table 73, pg165-166 of the MSAC application 1593.1 ADAR + In line commentary

Abbreviations: FTRCT = full-thickness rotator cuff tear; ICER = Incremental cost effectiveness ratio; QALY = Quality-adjusted life years
 * The commentary applied the following utility values (EQ-5D-5L score, Health level VAS) from Ruiz Ibán 2023 to conduct the additional sensitivity analysis: 0.68 at baseline and 0.78 at 12 months from REGENETEN group (Table 43, p103 of ADAR + in-line commentary) for successful surgery (Year 1) for REGEN ETN group in the model. The commentary extrapolated from 12 months to arrive at the utility of 0.80 for successful surgery in Year 2. The commentary assumed the utility for conservative management following re-tear to be the same as the utility of 0.68 at baseline. The commentary used the ADAR's method to calculate the utility for successful revision surgery/reverse arthroplasty following re-tear, i.e., assumed to be 80% of the average of the utility for successful surgery in the first 2 years (= average (0.78, 0.80) x 80% = 0.632). Note that ESC did not consider this sensitivity analysis clinically plausible.

14. Financial/budgetary impacts

The ADAR presented the financial implications of listing REGENETEN on the PL to private health insurers (PHIs), MBS and patients in Australia. The ADAR suggested that the current MBS items 48960, 48906 and 48909 relevant for the surgery for rotator cuff repair could be used for REGENETEN. However, the ADAR used an epidemiological approach to estimate the financial implications of REGENETEN as the market share approach was not feasible due to two of the three MBS items also being used for procedures other than rotator cuff repair such as shoulder reconstruction, resection and replacement services. This was reasonable.

Data sources used to estimate the financial implications.

The ADAR assessed the incidence of rotator cuff repair in the Australian population based on Paloneva et al., 2015²⁶, which reported incidence of 131 per 100,000 person-years for rotator cuff repair in 2011 based on the Finnish National Hospital Discharge Register. The ADAR claimed

²⁶ Paloneva, J., V. Lepola, V. Aarimaa, A. Joukainen, J. Ylinen and V. M. Mattila (2015). "Increasing incidence of rotator cuff repairs--A nationwide registry study in Finland." *BMC Musculoskeletal Disord* 16: 189.

that this incidence rate was justifiable based on Australian study which reported a population-adjusted rate of 150 procedures per 100,000 persons arthroscopic reconstruction of shoulder including rotator cuff repair and 165 procedures per 100,000 persons for both arthroscopy and open rotator cuff repair in the Western Australia (WA) Department of Health database for the period 2001-2013²⁷. Of note, both studies reported an increasing trend in rotator cuff repair. Hence, the commentary considered the incidence rate should be higher than the 131 per 100,000 person-years of rotator cuff repair as the data were more than ten years ago.

The ADAR assumed a linear increase in uptake of **redacted** of rotator cuff repairs per year for REGENETEN based on the uptake in other countries in the absence of information. The commentary considered the financial estimates based on the uptake rate were uncertain as the uptake rate was based purely on an assumption.

The proportion of PTRCT and FTRCT was based on an Australian cohort study Yeo et al., 2017²⁸ which reported 39% PTRCT and 61% FTRCT among 1624 patients who had undergone arthroscopic rotator cuff repair. The commentary considered this was reasonable. Of note, the previous application included prevalence of 71% PTRCT and 29% FTRCT and MSAC and Evaluation subcommittee (ESC) considered those values were uncertain.

The ADAR sourced data for the percentage point reduction in use of health resources for Population 2 (FTRCT) from the same source of data used in the economic model for Population 2. Hence, the issues identified in the transition probabilities inputs were also relevant for the financial calculations e.g., the ADAR sourced the probability of having revision RCR or reverse shoulder arthroplasty from the Parikh et al., 2021 study to calculate the percentage with conservative management after index procedure (please refer to Economic evaluation for Population 2 (FTRCT): Model transition probabilities, variables and extrapolation for more details).

Net financial impact on Private Health Insurance

For Population 1, using REGENETEN typically replaces the surgical sutures and anchors used in standard surgery. Therefore, funding the REGENETEN kit will save the costs associated with standard procedure of \$2,136 (Healicoil, footprint anchors and suture passer) to PHI. In Population 2, the use of REGENETEN is additional to standard repair. As such, the REGENETEN kit is an additional cost to PHI in the surgical procedure of rotator cuff repair. The cost-offsets from funding REGENETEN to Population 2 were from avoided costs associated with the management of patients following a retear as REGENETEN reduces the retear rate.

The estimated cost to PHI to fund REGENETEN is expected to grow from around **redacted** in Year 1 to **redacted** in Year 6. Considering cost-offsets, net costs to PHI are expected to reach \$1.4 million in Year 1 and rising to \$8.7million in Year 6. Offsets to PHI are expected to reduce the total costs by around **redacted** in Year 6. It was estimated that the cost to PHIs will be around **redacted** in Year 1, rising to **redacted** in Year 6. Table 18 summarised the net financial impact to PHIs with REGENETEN use in Population 1 (PTRCT) and Population 2 (FTRCT).

²⁷ Thorpe, A., M. Hurworth, P. O'Sullivan, T. Mitchell and A. Smith (2016). "Rising trends in surgery for rotator cuff disease in Western Australia." ANZ J Surg 86(10): 801-804.

²⁸ Yeo, D. Y., J. R. Walton, P. Lam and G. A. Murrell (2017). "The Relationship Between Intraoperative Tear Dimensions and Postoperative Pain in 1624 Consecutive Arthroscopic Rotator Cuff Repairs." Am J Sports Med 45(4): 788-793.

Table 18: Net financial implications of REGENETEN on PHI system – costs in \$millions*

Parameter	Calculation	Year 1 2024	Year 2 2025	Year 3 2026	Year 4 2027	Year 5 2028	Year 6 2029
Estimated use of REGENETEN							
Total estimated utilisation of REGENETEN**	A	redacted	redacted	redacted	redacted	redacted	redacted
Number of patients for Population 1 (PTRCT)	B=Ax39%	redacted	redacted	redacted	redacted	redacted	redacted
Number of patients for Population 2 (FTRCT)	C=Ax61%	redacted	redacted	redacted	redacted	redacted	redacted
Estimate cost impact to PHI							
Estimated cost of REGENETEN to PHIs for PTRCT patients*	D=Bx\$redacted	redacted	redacted	redacted	redacted	redacted	redacted
Estimated cost of REGENETEN to PHIs for FTRCT patients*	E=Cx\$redacted	redacted	redacted	redacted	redacted	redacted	redacted
Total estimated cost of REGENETEN to PHIs*	F=D+E	redacted	redacted	redacted	redacted	redacted	redacted
Change in use and cost of other health technologies							
Estimated cost offset to PHI in Population 1: PTRCT							
with standard of care savings*	G=Bx\$2,136	redacted	redacted	redacted	redacted	redacted	redacted
Estimated cost offset to PHI in Population 2: FTRCT							
Revision of RCT repair							
with avoided revision rotator cuff repair*	H = Cx4.4%x\$7,015	redacted	redacted	redacted	redacted	redacted	redacted
with avoided rehabilitation (physiotherapy costs) when using REGENETEN due to less revision rotator cuff repair*	I = Cx4.4%x\$1,980	redacted	redacted	redacted	redacted	redacted	redacted
Reverse total shoulder arthroplasty (RTSA)							
with RTSA when using REGENETEN*	J = Cx0.7%x\$22,484	redacted	redacted	redacted	redacted	redacted	redacted
with avoided physiotherapy when using REGENETEN due to less RTSA*	K= Cx0.7%x\$1,980	redacted	redacted	redacted	redacted	redacted	redacted
Conservative management (first year)							
with CM (physiotherapy) when using REGENETEN in the first year*	L = Cx12.4%x\$1,320	redacted	redacted	redacted	redacted	redacted	redacted
Conservative management (second year)							
Estimated cost offset to PHI with CM (physiotherapy) when using REGENETEN in the second year*	M = Cx14.2%x\$1,320	redacted	redacted	redacted	redacted	redacted	redacted
Estimated cost offset to PHI for Population 2 (FTRCT)*	N=H+I+J+K+L+M	redacted	redacted	redacted	redacted	redacted	redacted
Total estimated cost offset to PHI with REGENETEN*	O= G+N	redacted	redacted	redacted	redacted	redacted	redacted
Net financial impact to the PHI system*	P= F-O	\$1.38	\$2.77	\$4.20	\$5.67	\$7.18	\$8.73

Source: Table 79, pg175 and Table 80, pg176 of the MSAC application 1593.1 ADAR + In line commentary

Abbreviations: CM = conservative management; FTRCT = Full-thickness rotator cuff tear; PHI = Private health insurance; PTRCT = Partial-thickness rotator cuff tear; RTSA = Reverse total shoulder arthroplasty

Notes: *Cost in Australian dollar millions ** Total estimated utilisation of REGENETEN was calculated based on Australian population aged ≥18 years, Incident population undergoing rotator cuff repair, total rotator cuff repairs in the private setting and uptake rate.

Net financial impact to other health budgets

The ADAR claimed that the number of patients undergoing surgical repair for rotator cuff tears was not expected to be impacted by the introduction of REGENETEN. Therefore, MBS service volumes and costs MBS items 48960, 48906 and 489909 were not expected to change. The ADAR expected cost-savings for MBS, based on fewer retears with REGENETEN in Population 2. Table 19 summarised the net financial implications of REGENETEN to the MBS. Total savings to MBS was estimated at **redacted** in Year 1, rising to **redacted** in Year 6.

Table 19: Net financial implications of REGENETEN on the MBS – savings in \$millions*

Parameter	Calculation	Year 1 FY 2024- 2025	Year 2 FY 2025- 2026	Year 3 FY 2026- 2027	Year 4 FY 2027- 2028	Year 5 FY 2028- 2029	Year 6 FY 2029- 2030
Estimated utilisation of REGENETEN	A	redacted	redacted	redacted	redacted	redacted	redacted
Estimated utilisation of REGENETEN in Population 2	$B = A \times 61\%$	redacted	redacted	redacted	redacted	redacted	redacted
Revision of rotator cuff repair							
Estimated savings to MBS from reduction in patients requiring revision RCT repair *	$C = B \times 4.4\% \times \$1,057$	redacted	redacted	redacted	redacted	redacted	redacted
Reverse total shoulder arthroplasty (RTSA)							
Estimated savings to MBS from reduction in RTSA *	$D = B \times 0.7 \times \$2,876$	redacted	redacted	redacted	redacted	redacted	redacted
Conservative management – CM (first year)							
Estimated savings to MBS from reduction in patients requiring CM in the first year *	$E = B \times 12.4\% \times \$2,368$	redacted	redacted	redacted	redacted	redacted	redacted
Conservative management – CM (second year)							
Estimated utilisation of REGENETEN in their second year	F	redacted	redacted	redacted	redacted	redacted	redacted
Estimated savings to MBS from reduction in patients requiring CM in the second year *	$G = F \times 14.2\% \times \$2,368$	redacted	redacted	redacted	redacted	redacted	redacted
Shoulder MRI in patients with retear							
Estimated savings to MBS from avoided MRI due to reduced retear rate*	$H = B \times 17.5\% \times \318.30	redacted	redacted	redacted	redacted	redacted	redacted
Total savings to MBS when using REGENETEN*	$I = C + D + E + G + H$	\$0.12	\$0.03	\$0.46	\$0.62	\$0.78	\$0.90

Source: Table 81, p178 of the MSAC application 1593.1 ADAR + In line commentary

Abbreviations: CM = conservative management; FY = Financial year; MBS = Medical benefit scheme; MRI = Magnetic resonance imaging; PHI = Private health insurance; RTSA = Reverse total shoulder arthroplasty.

Notes: *Cost in Australian dollar millions

The ADAR also provided financial implications of REGENETEN to patients, based on lower proportion of patients requiring revision rotator cuff tear repair, reverse total shoulder arthroplasty or remaining in conservative management in Population 2. The ADAR claimed that the patients were expected to save (in out-of-pocket costs) from \$0.02 million in Year 1 and \$0.21 million in Year 6, with a higher uptake of REGENETEN (Table 20).

Table 20: Net financial implications of REGENETEN to the patients – savings in \$millions*

Parameter	Calculation	Year 1 2024	Year 2 2025	Year 3 2026	Year 4 2027	Year 5 2028	Year 6 2029
Estimated utilisation of REGENETEN	A	redacted	redacted	redacted	redacted	redacted	redacted
Estimated utilisation of REGENETEN in Population 2 (FTRCT)	$B = A \times 61\%$	redacted	redacted	redacted	redacted	redacted	redacted
Revision of rotator cuff repair							
Estimated cost offset to patients from avoid revision surgery*	$C = B \times 4.4\% \times \$1,538$	redacted	redacted	redacted	redacted	redacted	redacted
Reverse total shoulder arthroplasty (RTSA)							
Estimated cost offset to patients from avoided RTSA*	$D = B \times 0.7\% \times \784	redacted	redacted	redacted	redacted	redacted	redacted
Conservative management – CM (first year)							
Estimated cost offset to patients (out-of-pocket) from reduced CM (corticosteroid injections) - first year*	$E = B \times 12.4\% \times \390	redacted	redacted	redacted	redacted	redacted	redacted
Conservative management – CM (second year)							
Estimated utilisation of REGENETEN in the second year	F	redacted	redacted	redacted	redacted	redacted	redacted
Estimated cost offset to patients (out-of-pocket) from reduced CM (corticosteroid injections) - second year*	$G = F \times 14.2\% \times \390	redacted	redacted	redacted	redacted	redacted	redacted
Total savings to patients when using REGENETEN*	H = C+D+E+G	\$0.02	\$0.06	\$0.09	\$0.13	\$0.17	\$0.21

Source: Table 82, pg179 of the MSAC application 1593.1 ADAR + In line commentary

Abbreviations: CM = conservative management; FTRCT = Full-thickness rotator cuff tear; PHI = Private health insurance; RTSA = Reverse total shoulder arthroplasty.

Notes: *Cost in Australian dollar millions

The commentary considered the financial impact to PHI, MBS and patients were uncertain as the data used to calculate the percentage of patients receiving different management options after retear i.e., revision of rotator cuff tear repair, reverse total shoulder arthroplasty and CM were not relevant for the calculations as discussed earlier.

Uncertainty analyses of financial estimates

The ADAR presented uncertainty analyses based on key input parameters (Table 21).

Table 21: Sensitivity analyses – costs in \$millions*

Parameter	Year 1 2024	Year 2 2025	Year 3 2026	Year 4 2027	Year 5 2028	Year 6 2029
Base case						
Estimated utilisation of REGENETEN	redacted	redacted	redacted	redacted	redacted	redacted
Cost to the PHI*	redacted	redacted	redacted	redacted	redacted	redacted
Cost offset to the PHI*	redacted	redacted	redacted	redacted	redacted	redacted
Net financial impact to the PHI	redacted	redacted	redacted	redacted	redacted	redacted
Higher incidence: 165 rotator cuff repairs per 100,000 population						
Estimated utilisation of REGENETEN	redacted	redacted	redacted	redacted	redacted	redacted
Cost to the PHI*	redacted	redacted	redacted	redacted	redacted	redacted
Cost offset to the PHI*	redacted	redacted	redacted	redacted	redacted	redacted
Net financial impact to the PHI	redacted	redacted	redacted	redacted	redacted	redacted
Higher REGENETEN uptake 1: from redacted in year 1 to redacted in year 6						
Estimated utilisation of REGENETEN	redacted	redacted	redacted	redacted	redacted	redacted
Cost to the PHI*	redacted	redacted	redacted	redacted	redacted	redacted
Cost offset to the PHI*	redacted	redacted	redacted	redacted	redacted	redacted
Net financial impact to the PHI	redacted	redacted	redacted	redacted	redacted	redacted
Higher REGENETEN uptake 2: from redacted in year 1 to redacted in year 6						
Estimated utilisation of REGENETEN	redacted	redacted	redacted	redacted	redacted	redacted
Cost to the PHI*	redacted	redacted	redacted	redacted	redacted	redacted
Cost offset to the PHI*	redacted	redacted	redacted	redacted	redacted	redacted
Net financial impact to the PHI	redacted	redacted	redacted	redacted	redacted	redacted
Higher proportion of RCR performed by PHI: from redacted (base case) to redacted						
Estimated utilisation of REGENETEN	redacted	redacted	redacted	redacted	redacted	redacted
Cost to the PHI*	redacted	redacted	redacted	redacted	redacted	redacted
Cost offset to the PHI*	redacted	redacted	redacted	redacted	redacted	redacted
Net financial impact to the PHI	redacted	redacted	redacted	redacted	redacted	redacted

Source: Table 84, pg180-181 of the MSAC application 1593.1 ADAR + In line commentary

Abbreviations: PHI: Private Health Insurance; RCR = Rotator cuff repair

Notes: *Cost in Australian dollar millions

The main sources of uncertainty in the financial implications analysis were the incidence of rotator cuff repair and the extent of uptake of REGENETEN. The commentary identified issues with the data used to calculate these parameters, i.e., these parameters were either based on assumptions or irrelevant for the parameter of concern. Hence, the commentary considered the financial estimates provided in the ADAR highly uncertain.

15. Other relevant information

The ADAR included outsourced qualitative interviews and quantitative market research to supplement the evidence provided in the ADAR. The qualitative interviews conducted among six Australian orthopaedic surgeons specialising in rotator cuff repair and nine Australian GPs, of which, three were musculoskeletal specialists. The ADAR used direct quotes from orthopaedic surgeons throughout the ADAR to provide real-world context in support of the clinical and economic claims.

The quantitative component included 75 GPs. The commentary considered that this quantitative evidence did not support the clinical claim as these quantitative data were based mainly on the GPs' experience with rotator cuff tear patients, and whether they knew about medical device companies or new treatments. Of note, GPs considered surgery as the last option for patients with rotator cuff tears.

16. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues:

ESC did not consider the clinical claim of superiority of bovine bioinductive collagen implant (BCI) (REGENETEN) versus standard surgical repair was supported in either population, symptomatic partial-thickness rotation cuff tear (PTRCT, Population 1) or full-thickness rotator cuff tear (FTRCT, Population 2).

- While ESC appreciated the effort evident in the Applicant-Developed Assessment Report (ADAR) to present direct comparative evidence, ESC noted various limitations in the 3 randomised trials presented (e.g., Wang 2023 was unpublished, with small sample size, interim analysis at 3 months; Camacho Chacón 2024 included patients with FTRCT but was used to inform subpopulation 1 (PTRCT); Ruiz Ibán 2023 only had results at 12 months).
- ESC considered long-term safety and effectiveness uncertain.
- ESC noted that the reapplication continued to rely on imaging-based outcomes rather than patient-relevant functional outcomes and did not provide evidence to establish the correlation of radiological and functional outcomes, the importance of which was emphasised by MSAC at its November 2020 meeting and reiterated by PASC in August 2023.
- ESC noted the ADAR did not include continued conservative management (CM) as additional comparator for Population 1 (PTRCT), as advised by PASC in August 2023. ESC considered a non-surgical comparator such as CM should be included, as patients can elect to not have surgery. ESC also considered it important to outline what CM involves for patients.
- ESC recommended that the applicant should provide evidence that shows stronger correlation of radiological outcomes with functional outcomes (if radiological outcomes were still considered to be a key point).

Economic issues:

- ESC noted the low correlation in measures of 'success' used in Population 1 and 2 models. ESC considered while the presence of high re-tear rates does not necessarily preclude improvements in American Shoulder and Elbow Surgeons (ASES) scores, a consistent approach combining functional and magnetic resonance imaging (MRI) outcomes would be more robust.
- Some key issues with the economics that were identified by MSAC in the previous application have only been partially addressed by the reapplication. These include
 - the lack of high-quality evidence that creates uncertainty in the clinical effectiveness, which leads to key uncertainties in the economic evaluation.
 - uncertain long-term effectiveness: and low correlation between the different effectiveness measures used for the two populations (potentially introducing bias)
- Several structural issues with the models remain, including the lack of consideration for downstream costs for partial-thickness tears (population 1). A consistent approach incorporating both functional and imaging measures for both populations would be more appropriate.

Financial issues:

- The ADAR presented a new budget impact model, but issues with the relevance of some of the data and assumptions about uptake mean that the financial estimates are uncertain. Utilisation may be higher than predicted based on the wording of the restriction.
- The cost of the REGENETEN kit is high and has not been reasonably justified.

Proposed listing:

- ESC agreed with the commentary that the proposed implant should be limited to once per shoulder, which the applicant supports. However, the department will need to consider how to restrict multiple use, as there is no MBS item number for REGENETEN.

ESC discussion

ESC noted that the application was a reapplication from Smith & Nephew Pty Ltd requesting the listing of a bovine bioinductive collagen implant (BCI) (REGENETEN) for the repair of rotator cuff tears on the Prescribed List of Medical Devices and Human Tissue Products (PL).

ESC noted MSAC first considered the application (MSAC application 1593) at its July 2020 meeting but did not support public funding for the proposed device at the time. MSAC noted the Applicant-Developed Assessment Report (ADAR) for application 1593 relied on naïve indirect comparisons to inform comparative safety and clinical effectiveness of BCI versus standard surgical repair. MSAC therefore considered the evidence base of low quality, with highly uncertain comparative safety, clinical and cost-effectiveness relative to standard surgical repair in both subpopulations of symptomatic partial and full thickness tears.

Clinical issues**Uncertain long-term safety and effectiveness**

ESC noted the ADAR presented direct comparative evidence: 2 randomised controlled trials (Wang et al. 2023, Camacho-Chacon et al. 2023) for Population 1 (PTRCT) and 1 randomised trial (Ruiz Ibán et al. 2023) for Population 2 (FTRCT).

ESC noted that both Wang 2023 and Camacho-Chacon 2023 were unpublished at the time of assessment. All trials had small sample size (N = 26 to 120) and short follow-up (3 to 24 months). In addition, ESC noted that multiple outcomes at multiple endpoints were reported in the trials, including the Western Ontario Rotator Cuff (WORC) Index, the American Shoulder and Elbow Society (ASES) score and the Single Assessment Numeric Evaluation (SANE) score. ESC noted that results were different when different outcome measures were used, rendering interpretation of the trials results difficult.

ESC noted that the trials did not include many older patients, who tend to have a high incidence of rotator cuff injuries. ESC considered that there was the potential for older people who receive the treatment requiring more care, including post-surgery physiotherapy, and this was not considered. Also not considered was the risk to quality of life (QoL) for people who are very invested and have the procedure, but it is not successful.

ESC noted that the Australian Rotator Cuff (ARC) study, which is comparing arthroscopic surgery with repair of rotator cuff to surgery without repair of rotator cuff (placebo surgery), is due for completion in 2025. This may provide more evidence for the surgical comparator.

ESC noted that the trials reported no difference in safety between REGENETEN and surgery. This included complications in hospital indicators (death, re-admission, length of stay), instances of steroid injection/antibiotics, re-tears or additional surgery, rates of adhesive capsulitis, and

serious adverse events of failure of repair and revision surgery, infection and cardiac death. Based on this evidence, ESC agreed that REGENETEN appeared to have non-inferior safety compared to surgery, but due to the short follow-up in the presented studies, the long-term safety (beyond 12–24 months) was uncertain.

Regarding comparative effectiveness, ESC noted that the Wang et al. 2023 trial reported superior WORC scores with REGENETEN at 6 weeks and 3 months compared to surgery. It also reported superior ASES and SANE scores with REGENETEN at 6 weeks compared to surgery, but there was no difference at 3 months. However, due to the small numbers and very short follow-up, ESC considered that the long-term effectiveness was uncertain. ESC noted that the ADAR used other case series to support outcomes at 3 months and translated to 2 and 5 years, but ESC considered this inappropriate.

ESC noted that Camacho-Chacon et al. 2023 (population 1) was a Spanish trial involving a single surgeon and 60 patients. Although the population had full-thickness tears, the tears were stable, so the surgical treatment was similar to that for partial-thickness tears. The ADAR therefore classed this study as relevant for population 1. ESC noted the commentary's criticism about this population being used in the economic evaluation for population 1, considering it not relevant as the patients had full-thickness tears. ESC considered that the uncertainty in the evidence is increased because of the underlying differences in the Camacho-Chacon et al. cohort and the Wang et al. cohort (as an example, partial-thickness tear patients have been found to have higher pain levels, based on PASC advice), but the intervention is consistent with the clinical pathway for partial tears in that it is an isolated implant used instead of sutures, rather than in addition to (as is done for the full-tear model). However, the use of REGENESORB anchors in the comparator (as an adjunct) in the Camacho-Chacon et al. study introduces an additional variable that might confound the comparison; therefore, this comparison may not be directly applicable. ESC also noted from the policy paper that the trial population differs from the proposed patient population, who only require 3 months of CM. Although the ADAR describes spontaneous healing of rotator cuff tendon injuries as rare, this may still be relevant given the lack of a 1:1 correlation between rotator cuff tears and symptoms.

ESC noted that the Camacho-Chacon et al. 2023 study showed ASES scores were superior with REGENETEN over surgery at all time points, but the absolute difference decreased with longer follow-up. The Constant–Murley Score (CMS) was also superior with REGENETEN at all time points up to 24 months, but there was no difference in visual analogue scale (VAS) pain scores. Compared to surgery, REGENETEN was shown to have lower sling time (12.5 days vs 27 days), fewer physical therapy visits (6 vs 10) and faster return to work (90 days vs 163.5 days). The tendon was also thicker at all time points up to 24 months.

ESC noted from the pre-ESC response that the Camacho-Chacon et al. study was published in May 2024. The primary outcome of the published study was biopsy and MRI “tendon quality” at 6 months, with patient-reported outcomes being a secondary outcome. ESC noted that there were no re-tears over 24 months for either REGENETEN or standard surgery. Additionally, although REGENETEN had higher median ASES scores than surgery at each time point, the proportion of patients meeting the minimal clinically important difference (MCID) was similar between groups. There were similar results for CMS: REGENETEN had higher median scores at each time point, but by 12 months, patients in both groups met the MCID. Furthermore, ESC noted that the study did not perform a formal sample size calculation, and it stated that a “24-month follow-up may be considered a limitation”.

ESC noted that the Ruiz Ibán et al. 2023 study (population 2) reported on transosseous full-thickness tendon repair with and without REGENETEN. The primary endpoint was re-tear rates at 1 year defined by radiological MRI endpoint (Sugaya classification 4 or 5), which were shown to

be significantly lower with REGENETEN than with surgery (8% vs 25.8%; $p = 0.01$). ESC noted that there were no differences in Brief Pain Inventory scores at any time point up to 12 months, or in CMS/ASES and EQ-5D-5L results up to 12 months. ESC noted that the ADAR inferred that avoidance of re-tear is associated with better clinical outcomes.

ESC noted that the pre-ESC response reported that extra data from the Ruiz Ibán et al. 2023 study showed that 2-year re-tear rates were also lower with REGENETEN (12.3% vs 35.1% for surgery), but no reference was provided for this. The pre-ESC response also argued that radiological tendon “re-tear” patients have worse patient-reported outcomes than “healed” tendons and inferred that REGENETEN patients will more likely have better patient-reported outcomes than the comparators. However, ESC noted that there was still no evidence provided to correlate functional outcomes with radiological outcomes.

Imaging-based outcomes

ESC noted that the ADAR continued to rely on imaging-based outcomes as a functional surrogate, despite having patient-reported outcomes available in the trials. ESC recalled that MSAC had previously considered the use of radiological improvement as the main outcome inappropriate and advised that the focus should be on pain and functional improvements ([MSAC 1593 PSD, July 2020 MSAC meeting](#)). ESC reiterated the importance of functional outcomes, noting that people with tears can be asymptomatic.

ESC also recalled that MSAC had previously considered that the use of magnetic resonance imaging (MRI) to diagnose re-tear may be problematic, but this issue remains unresolved.

ESC recommended that the applicant should provide evidence that shows stronger correlation of radiological outcomes with functional outcomes (if radiological outcomes were still considered to be a key point).

Continued conservative management as additional comparator (PTRCT)

ESC noted the ADAR did not include continued conservative management (CM) as additional comparator for subpopulation 1 (PTRCT), as advised by PASC in August 2023.

ESC noted the applicant initially requested an expedited pathway assessment as the proposed PICO aligned closely with the Ratified PICO confirmation for MSAC application 1593 (September 2019). MSAC Executive however, advised in April 2023 that consideration by the PICO Advisory Sub-committee (PASC) was required particularly to define the duration of failure to CM in the eligible population and to consider continued CM as an additional comparator for Population 1 (PTRCT). PASC subsequently considered a time frame of a minimum of 3 months of CM as an eligibility criterion reasonable (p6, Ratified PICO Confirmation, August 2023 PASC meeting). ESC also recalled that PASC advised to include CM as additional comparator in Population 1, noting a proportion of patients who delay surgery but then get better and that more patients may now opt for surgery due to the lower burden of rehabilitation post-surgery (p16, Ratified PICO Confirmation, August 2023 PASC meeting).

ESC noted the applicant’s Pre-ESC Response reiterated its arguments against the inclusion of continued CM as an additional comparator for Population 1 (PTRCT). However, ESC considered that a non-surgical intervention such as CM should be included as a comparator, as patients can elect to not have surgery. ESC noted that a 2019 Cochrane review²⁹ of randomised controlled trials (RCTs) of surgery for rotator cuff tears shows that it is uncertain if surgery provides clinically meaningful benefit to people with symptomatic tears. Additionally, a study by Littlewood et al.

²⁹ Karjalainen TV, Jain NB, Heikkinen J, Johnston RV, Page CM and Buchbinder R (2019). [Surgery for rotator cuff tears](#). *Cochrane Database of Systematic Reviews* 12:CD013502.

(2023)³⁰ shows that increased access to physiotherapy-led exercise may decrease the need for surgery. ESC also considered it important to include data or narrative on what CM involves for a patient, noting that:

- access to public outpatient physiotherapy for this indication is likely poor.
- there are very few MBS-funded physiotherapy sessions if using a chronic disease management plan, so out-of-pocket costs are likely.
- there is no accepted protocol for physiotherapy for pre- or post-surgery rehabilitation, or CM without surgery.

Treatment is conservative management (CM; analgesia, anti-inflammatories, physical therapy) or surgery. Surgery can include debridement/bursectomy +/- surgical repair of any of the four shoulder muscles and its tendons with sutures and anchors.

ESC considered a non-surgical comparator such as CM should be included, as patients can elect to not have surgery. ESC also considered it important to outline what CM involves for patients. ESC also suggested that the applicant provide some discussion on natural history of the condition, as this would be helpful for decision-making.

Economic issues

ESC noted that the ADAR's economic evaluation had changed substantially from the original application considered at the July 2020 MSAC meeting. In the original application, partial- and full-thickness tears were modelled together using expected value analysis. In contrast, the current reapplication used 2 separate decision tree models for each population, both using a time horizon of 2 years but different outcomes and analyses:

- For Population 1 (PTRCT): a cost-effectiveness analysis using change in MCID (15.5 units) of ASES scores as the outcome and two health states in the model (MCID change in ASES score from baseline, and no MCID change in ASES score from baseline).
- For Population 2 (FTRCT): a cost-utility analysis (based on a recent publication by McIntyre et al. 2023) using quality-adjusted life years (QALYs) based on rates of re-tear and subsequent repair as the outcome and five health states in the model (tear heals; tear fails to heal followed by revision surgery and tear heals; tear fails to heal followed by revision surgery and tear fails to heal; tear fails to heal followed by reverse total shoulder arthroplasty; and tear fails to heal followed by continued CM).

Low correlation in effectiveness measures between Population 1 and Population 2

ESC was concerned that there was low correlation in the effectiveness measures used to determine treatment "success" between the models used for the two populations.

ESC noted that in the model for population 1, everyone "succeeds" by 12 months because in both trials (partial- and full-thickness tears), mean ASES scores continue to increase over time despite re-tear rates – ASES scores are subjective and calculated based on 50% pain (VAS) and 50% function, so the presence of high re-tear rates does not necessarily preclude improvements in ASES scores. ESC noted that the ADAR argued that ASES scores are considered an important functional outcome of effectiveness. However, ESC noted that multiple factors, including partial healing, effective pain management, timing of assessments and variations in the severity of re-tears, can contribute to increased ASES scores despite structural failures – these factors are important to consider when interpreting the outcomes of rotator cuff repair trials.

ESC noted that, based on ASES averages, 100% of patients in population 2 would also reach "success", and this generates QoL gains over time. However, based on re-tear rates (applied in

³⁰ Littlewood C, Moffatt M, Beckhelling J, Davis D, Burden A, Pitt L et al. (2023). [Physiotherapist-led exercise versus usual care \(waiting-list\) control for patients awaiting rotator cuff repair surgery: a pilot randomised controlled trial \(POWER\)](#). *Musculoskeletal Science and Practice* 68:102874.

the population 2 model), between 8% and 25.8% of patients fail. This presents a situation of “success” in one outcome and “failure” in another, noting that “failure” generates QoL decrements and additional downstream costs. The implication is that a model based on ASES scores alone vs tear heal alone will generate quite different modelling results.

ESC considered that a more consistent approach to modelling both populations would have been more appropriate and robust (with multiple factors such as patient function, symptoms and MRI, as per clinical practice).

Population 1 (PTRCT)

The ADAR reported that using standard surgical repair with REGENETEN in patients with symptomatic PTRCT who have failed at least three months of CM would result in an incremental benefit of 0.58 unit of MCID of ASES gained over a 2-year period when compared to standard surgical repair without REGENETEN, resulting in an ICER of **redacted** per MCID of AES (15.5 points in the ASES score) gained.

ESC considered the results of the ADAR’s base case analysis for population 1 highly uncertain because the Camacho-Chacon et al., 2023 trial included FTRCT patients to inform the economic evaluation. ESC considered increased the uncertainty of evidence in terms of the underlying differences in these groups. ESC noted the intervention arm of the Camacho-Chacon et al., 2023 trial is consistent with the clinical pathway for partial tears in that it is an isolated implant used instead of sutures, rather than in addition to (full tear model). However, the inclusion of the use of REGENESORB anchors in the comparator (as an adjunct) introduces an additional variable that might confound the comparison and as such this comparison may not be directly applicable.

ESC noted the commentary considered the ADAR inaccurately calculated the change in ASES score and inappropriately used the number of unit changes in MCID of ASES as the outcome of the cost-effectiveness analysis. ESC noted the commentary used the same approach as in the ADAR but an alternative method of calculation of change in MCID of ASES scores resulted in a substantial reduction in incremental benefit of standard surgical repair with REGENETEN to 0.065 unit of MCID of ASES gained over a 2-year period and the ICER increased to **redacted** per MCID gained.

ESC noted that the Pre-ESC Response acknowledged that there are different methods to estimate average gains in MCID over 2 years using the trial and accepted the alternative methodology by the commentary. ESC considered the commentary’s approach reasonable but agreed with the pre-ESC response that the commentary should have added the gains in MCID for each period to get the total gain for the entire period of 24 months. ESC noted that after correcting the error in the re-specified base-case, the incremental benefit became 0.465 per MCID of ASES score and the ICER became **redacted** per unit MCID of ASES gained (Table 11).

ESC noted that the main driver of the model for population 1 is the incremental difference in MCID of ASES scores – specifically, the 3.3% of patients who received standard surgical repair without REGENETEN who did not reach MCID until 12 months. However, ESC noted that the decision-tree pathway does not accurately depict the clinical pathway. ESC considered the two health states (change in MCID of ASES scores and no change in MCID of ASES scores) to be inappropriate, as there is no decision made and all patients receive the same cost and effectiveness irrespective of the MCID outcome. Additionally, ESC noted that the model does not include any downstream costs (including for revision and repair following re-tear, which the literature suggests represents up to 21% of patients in the treatment arm) or benefits. It also assumes no failure (progressed tear) in 24 months, which ESC considered to be clinically unrealistic.

ESC noted that the sensitivity analyses using the corrected re-specified base case analysis

showed that:

- decreasing the MCID for ASES scores to 6.4 (minimal value of the six included studies in the systematic review by Jones et al. 2020³¹) decreased the ICER to **redacted** /MCID of ASES scores gained.
- increasing the MCID to 21.9 (maximal value of the six included studies in the systematic review) increased the ICER to **redacted** /MCID of ASES gained.

Population 2 (FTRCT)

For population 2 a cost utility analysis was presented using a decision tree model that was based on a recent publication by McIntyre et al., 2023 and the model was modified to include QALYs as the health outcome. ESC noted the model relied on utility values of 'success' from clinical estimates of both PTRCT and FTRCT patients, when population 2 is patients with FTRCT. ESC considered this introduced uncertainty due to underlying difference in these patient groups. ESC noted that the utility values of the trial were not used as they were the average per treatment pathway over time, and not disaggregated into tear and re-tear. Therefore, clinical estimates from the study by Grobet et al. [2020]³² were used instead. ESC considered the estimates in the ADAR to be an appropriate proxy and did not support the utility values proposed in the commentary sensitivity analysis – notably, the assumption that the utility of patients with incomplete healing and then successful revision surgery would be lower than CM was clinically implausible. ESC noted that the revision utility was not measured in the Grobet et al. study, so the model makes assumptions about the re-tear pathway (such as 80% of first successful surgery) based on other clinical literature, which ESC considered reasonable. The model also assumed that:

- patients with CM after surgery and failure do not improve, but ESC considered that there was evidence that CM can lead to improvement, and this was tested in a sensitivity analysis.
- the costs of REGENETEN are incremental and would be claimed in addition to standard surgical repair. PASC had noted that, in population 2, the implant would be used in addition to the standard repair.
- there is no difference in costs for different comparator treatments (arthroscopic vs mini surgery), which are used interchangeably. However, ESC noted that these procedures have different durations.

ESC noted that the Pre-ESC Response acknowledged a misspelling in Table 67 of the ADAR which in its 3rd row reads “Tear fails to heal (2nd year)” should be “Tear heal (2nd year)” instead.

ESC noted that the base case ICER for population 2 was **redacted** /QALY. ESC noted that a key driver of the model for population 2 is the incremental difference in tear healing rates. The model assumes that tear heal (re-tear rates) equates to procedure success, and those who fail do not incur any QOL benefits from the first procedure and maintain pre-operation utility until second-line treatment. A study by Iannotti et al. 2013³³ found that re-tears following rotator cuff repair primarily occurred between 6 and 26 weeks, with a substantial number of re-tears occurring between 12 and 26 weeks; ESC considered this conservative. ESC noted from sensitivity analyses in the ADAR that:

- increasing the rate of tear heal failure for REGENETEN to 18.1% increases the ICER to **redacted**
- decreasing the rate of tear heal failure for standard of care to 16.6% increases the ICER to **redacted**

³¹ Jones IA, Togashi R, Heckmann N and Vangsness CT Jr (2020). [Minimal clinically important difference \(MCID\) for patient-reported shoulder outcomes](#). *J Shoulder Elbow Surg* 29(7):1484–1492.

³² Grobet, C., L. Audige, K. Eichler, F. Meier, B. Brunner, S. Wieser and M. Flury (2020). "Cost-Utility Analysis of Arthroscopic Rotator Cuff Repair: A Prospective Health Economic Study Using Real-World Data." *Arthrosc Sports Med Rehabil* 2(3): e193-e205.

³³ Iannotti JP, Deutsch A, Green A, Rudicel S, Christensen J, Marraffino S et al. (2013). [Time to failure after rotator cuff repair: a prospective imaging study](#). *J Bone Joint Surg Am* 95(11):965–971.

- increasing the utility value of CM after tear heal failure to 0.781 increases the ICER to **redacted**
- increasing the cost of the REGENETEN kit by 20% (to **redacted**) increases the ICER to **redacted**.

ESC also recalled that, in its previous consideration of the original application, MSAC considered the definitions of “re-tear”, “incomplete healing” and “treatment failure” to be unclear. ESC considered that this issue remains unresolved.

ESC noted the pre-ESC response acknowledged that the utility value of 0.950 for the second year of the health state ‘tear heal’ was higher than the population norm for the Australian general population of 0.90 (population age between 45 and 64 years old), noting that a sensitivity analysis using the same utility value of 0.891 for both first and second year of tear heals resulted in an ICER of **redacted** per QALY gained.

Financial issues

ESC noted that an epidemiological approach was used to estimate the financial impacts, with the uptake rate increasing over time. The number of patients was not expected to be impacted by the introduction of REGENETEN; however, ESC considered that there was the potential for overutilisation.

ESC noted that the total savings to the MBS were estimated as \$120,000 in year 1, increasing to \$900,000 in year 6. For population 2, fewer re-tears equated to reduced cost revisions for rotator cuff tear repair and reverse total shoulder arthroplasty, and a decrease in the use of MRI to diagnose retears and CM costs. Patients were expected to save (in out-of-pocket costs) from \$20,000 in year 1 to \$200,000 in year 6, with a higher uptake of REGENETEN. However, ESC noted that the financials are sensitive to incidence, re-tear rates and increasing uptake rate. ESC also considered that, because some people with tears can be asymptomatic, the true incidence of rotator cuff injuries is not known. ESC also considered that there is a risk of imaging being performed by clinicians without adequate skills to do so, resulting in people being referred for surgery unnecessarily. The complexity of therapy required for shoulder injuries may also drive more people to have surgery.

Proposed listing

ESC noted that this application is not seeking a new Medicare Benefits Schedule (MBS) item number; REGENETEN will be used with existing surgical item numbers 48960 (the most used item; fee of \$1,036.25), 48906 and 48909. ESC noted that the existing surgical MBS items do not restrict access to once per shoulder, and that the included studies only use once per shoulder. ESC considered that a usage limit should be in place to avoid leakage, noting that the applicant’s pre-ESC response was agreeable to a restriction of “once per shoulder (not tendon) per lifetime”. ESC noted that default PL listing arrangements do not restrict PL benefit payments to use in the populations approved via the MSAC process. ESC considered it reasonable that the PL billing code limit the use of REGENETEN to rotator cuff tendon injuries (as is the case for its entry on the Australian Registry of Therapeutic Goods), and that the PL conditions restrict benefit claims with the specific surgical MBS item numbers (48960, 48906, 48909). ESC also considered it unclear whether “failure” (called a device-related adverse event) of the procedure is a one-time claim or is eligible for multiple claims (at the discretion of the surgeon).

ESC noted that the ADAR priced the REGENETEN kit at **redacted** (base case), which the ADAR estimated would save \$2,136 in standard surgery costs (based on estimated costs for the replacement of anchors and sutures). ESC noted the ADAR did not specify if the proposed PL benefit for the REGENETEN kit is based on the public sector reference price or, if not available, international pricing data. ESC noted that the price of the kit is a key driver in the cost-

effectiveness and financial estimates.

ESC considered that both anaesthesia consultation (MBS item 17615) and anaesthesia items (MBS 23010, 23025, 23035 depending on the length of anaesthesia) may be associated with the surgical repair. ESC noted that these items were not directly used in the economic evaluation of either population.

Consultation feedback

ESC noted and welcomed consultation input from two (2) professional organisations and seven (7) individuals, all of whom were specialists. ESC noted that consultation feedback from specialist surgeons was positive, stating that REGENETEN provides improved patient outcomes which include excellent pain relief, good early range of motion, shorter rehabilitation period and return of function. However, some feedback also raised concerns about the risk of REGENETEN being used multiple times in many areas of the body, which would directly impact private health premiums for patients. The feedback also disagreed with the costings provided by the applicant and highlighted that there was ample time for the applicant to get better evidence for effectiveness. Additionally, access to conservative management (CM) for Australian patients was not discussed, nor was how REGENETEN would impact access to, and spending on, CM. Finally, there was concern about the abundance of direct-to-consumer marketing for the product overseas, and the potential that consumers were inflating the benefits and asking for the technology despite the lack of clinical evidence.

17. Applicant comments on MSAC's Public Summary Document

Smith+Nephew is disappointed with MSAC's decision not to recommend the REGENETEN bioinductive collagen implant (BCI) for the repair of rotator cuff tears but welcome the advice for an expedited re-application pathway. Despite this, the Sponsor reiterates their concerns about the presentation of MSAC's advice in this PSD, as it may be perceived as misleading, particularly due to the inclusion of the incomplete and irrelevant ARC study, along with analyses from PHA (insurers) and PrecisionMed, which lack the necessary validation and relevance. Furthermore, the directive to compare REGENETEN to the continued 'Conservative Medical Management (CMM)' which has already been deemed "failed" as part of patient population criteria, is inappropriate as it does not align with the standard of care which is rotator cuff repair (RCR). REGENETEN is intended for patients seeking surgical solutions after exhausting CMM, not as a replacement for CMM. The Sponsor refutes MSAC's claims about uncertain comparative safety, citing three randomised controlled trials confirming that REGENETEN does not pose any incremental risk beyond the standard surgical repair (two with two years of follow-up) and noting positive consultation feedback from Australian surgeons, along with over 160,000 successful implantations globally in the past ten years. It is acknowledged that there are no safety concerns with the device itself. Moreover, MSAC's advice is inconsistent with views reached by other HTA reviewers, such as the ECRI in the USA and HAS in France, both of whom recognise the benefits of REGENETEN over the standard of care and have raised no concerns about safety in their assessments. Japan's Central Social Insurance Medical Council (Chuikyo) has likewise confirmed the safety and effectiveness of REGENETEN, providing national funding since June 2023.

18. Further information on MSAC

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