Australian Government

Medical Services Advisory Committee

# Public Summary Document

## *Application No. 1593 – Bovine bio-inductive collagen implant (REGENETEN™) for repair of rotator cuff tear*

**Applicant:** **Smith & Nephew Pty Ltd**

**Date of MSAC consideration:** **MSAC 79th Meeting, 28-29 July 2020**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

### 1. Purpose of application

An application requesting Prostheses List listing of bovine bioinductive collagen implant (REGENETEN™) for the repair of rotator cuff tear was received from Smith & Nephew Pty Ltd by the Department of Health.

### 2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC did not support public funding for bovine bioinductive collagen implant (REGENETEN) for the repair of rotator cuff tear. MSAC will advise the Prostheses List Advisory Committee (PLAC) that it considered the evidence for comparative safety and effectiveness to be highly uncertain relative to standard surgical repair in both subpopulations (symptomatic partial and full thickness tears), and as a consequence, the incremental cost-effectiveness was also uncertain.

| **Consumer summary** |
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| Smith & Nephew Pty Ltd made an application to the Prostheses List Advisory Committee (PLAC) to list a bovine bioinductive collagen implant (REGENETEN) on the Prostheses List (PL) to repair rotator cuff tears. PLAC requested that MSAC perform a health technology assessment for REGENETEN to determine its comparative effectiveness, safety and cost-effectiveness.<br><br>The rotator cuff is a group of muscles and tendons around the shoulder joint. Damage to the rotator cuff, such as a tear in a tendon, can cause shoulder pain and weakness.<br><br>REGENETEN is implanted during shoulder surgery to provide a layer of collagen over injured tendons. It is meant to provide a base on which the body can grow new tissue to repair the tendons. |

**Consumer summary**

The application was for two types of tears: chronic partial tears and full tears, which have not healed on their own after 3 months of standard care. This application was not for tears due to acute injury or trauma.

MSAC noted that there were no studies directly comparing REGENETEN with standard care, which makes effectiveness and safety difficult to assess. Further, the studies that did exist were of low quality. Using magnetic resonance imaging (MRI), it looked like the tendons repaired with REGENETEN were healing better than those without REGENETEN. However, REGENETEN patients did not report any significant improvements in pain or function in their injured shoulder. Further, REGENETEN appeared to be associated with some adverse events, such as infection and allergic skin reactions. MSAC considered that less pain and better function were more important outcomes than an improved MRI scan from a patient's point of view.

Because the effectiveness and safety were uncertain, MSAC could not say whether REGENETEN was cost-effective.

**MSAC's advice to PLAC**

MSAC advised PLAC that REGENETEN's comparative effectiveness, safety and cost-effectiveness were all uncertain due to low-quality evidence. MSAC also disagreed with the application focusing on MRI results as a main outcome. It considered that patient-reported outcomes such as pain and function were more appropriate; and that compared with standard surgery, these outcomes did not improve after surgery with REGENETEN.

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

MSAC noted that this application came from PLAC, which requested that MSAC perform a full health technology assessment for the listing of bovine bioinductive collagen implant (REGENETEN™) on the Prostheses List (PL) for the repair of rotator cuff tear. MSAC noted that REGENETEN is not currently funded or reimbursed in the private or public setting.

MSAC noted the application was for two subpopulations:

1. Patients with symptomatic partial-thickness rotator cuff tear (PTRCT) who have failed at least three months of conservative (non-surgical) management and are considered eligible for (or indicated for) surgical repair

2. Patients with symptomatic full-thickness rotator cuff tear (FTRCT) who have failed at least three months of conservative (non-surgical) management and are considered eligible for (or indicated for) surgical repair.

MSAC noted that the Applicant Developed Assessment Report's (ADARs) treatment algorithm proposes that REGENETEN is an alternative to surgical repair for patients with PTRCTs and in addition to surgical repair for patients with FTRCTs.

MSAC noted that the ADAR relied on low-quality evidence from naive indirect comparisons to derive estimates of the comparative effectiveness and safety of REGENETEN versus standard surgery in both subpopulations. The REGENETEN studies had small sample sizes (<30) and a high risk of bias. The ADAR presented meta-analyses for each population, and MSAC noted that the indirect comparisons did not have a common comparator and were not

adjusted. The standard surgery studies were also highly heterogeneous, especially for FTRCTs.

MSAC noted the procedural complications and adverse events reported post-surgery:

- For PTRCTs using REGENETEN: 0–9.1% rate, including cardiac ablation, allergic skin reaction, wound drainage due to stitch abscess
- For PTRCTs using standard surgery: 0–7.1% rate, including adhesive capsulitis
- For FTRCTs using REGENETEN: 0–3.6% rate, including post-operative infection, deep vein thrombosis, graft remaining and loosening in bursa at 4 months post-surgery.

Adverse events were not reported in the studies for standard surgery in patients with FTRCTs. 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). MSAC noted the applicant highlighted concerns of publication bias among standard surgery studies, which would bias against REGENETEN.

MSAC noted that there were statistically significant improvements in imaging outcomes for REGENETEN compared with standard surgery for both subpopulations. However, MSAC also noted that the imaging results were problematic due to the lack of definitions for "retear", "incomplete healing" and "treatment failure".

MSAC considered using imaging results as the primary outcome to be inappropriate, as there is no evidence to support correlating imaging results to patient-reported outcomes (PROs), or to predict a reduced rate of osteoarthritis. 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 (e.g. American Shoulder and Elbow Surgeons Shoulder Score [ASES]) or pain (Russell et al. 2014[1]), and many tears do not progress if left unrepaired. MSAC considered the core outcomes (pain reduction, function and adverse events) to be the most important outcomes. MSAC agreed with the pre-MSAC response that proof of repair is important, but not as important as the core outcomes.

MSAC noted that there were no statistically significant differences in the pooled risk for core functional outcomes for REGENETEN and standard surgery for either subpopulation over 12–24 months follow-up. MSAC considered that the results trended towards better PROs for standard surgery. MSAC noted no power calculations were undertaken for REGENETEN studies, as they were case series data, and that there is some contention about the minimal clinically important difference for the ASES. Overall, MSAC considered the evidence to be low quality, leading to low confidence in the effect estimate.

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. The economic model assumes non-inferior safety, which is uncertain, and superior functional outcomes, for which there is no evidence. The ADARs model relied heavily on imaging outcomes, which MSAC considered to be inappropriate. MSAC also agreed with ESC, which noted several other structural issues with the model. MSAC noted that the

[1] Russell RD, Knight JR, Mulligan E, Khazzam MS. Structural integrity after rotator cuff repair does not correlate with patient function and pain: a meta-analysis. JBJS. 2014 Feb 19;96(4):265-71.

Commentary's respecified base case model attempted to address some of these issues resulting in much higher incremental cost-effectiveness ratios (ICERs) for both subpopulations in the base case (see Table 9) and sensitivity analysis (see Table 10) and scenario analyses (see Table 12).

MSAC considered the ADARs original estimate of prevalence of PTRCT (71%) *vs.* FTRCT (29%) to be uncertain, which had an impact on pooled ICERs. MSAC also noted the pre-MSAC response, which the applicant aimed to provide more certainty around the updated prevalence estimate from an Australian retrospective study (PTRCT: 39%; FTRCT: 61%).

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 Medicare Benefits Schedule (MBS) items, and showed that the total budget impact may be 20% higher in the respecified base case financial model than that presented in the ADAR (see Table 15).

MSAC noted the upcoming cohort study that would provide comparative evidence of REGENETEN *vs.* standard surgery in PTRCT (NCT03734536). MSAC also noted the primary outcome was ASES, but the study is now delayed (until possibly 2022). However, MSAC considered that the applicant would need to provide high quality evidence before they could resubmit to MSAC.

***Other discussion***

MSAC noted the uncertainty around surgical repair for these types of injuries, as they tend to improve over time. MSAC noted from high certainty evidence (2 trials; n=284) that decompression for rotator cuff disease (including PTRCTs) does not provide clinically important benefits over placebo in pain, function or health-related quality of life (Karjalainen et al. 2019[2]). MSAC also noted from moderate to low certainty evidence (3 trials; n=258) that surgery for FTRCTs was not superior to non-operative treatment, and also there was no added benefit of decompression during surgery (Karjalainen et al. 2019[3]). Thus, MSAC recommended that the MSAC Executive review the MBS item 48903 for shoulder subacromial decompression surgery.

MSAC also noted that surgical repair of PRCTs is not standard practice other than for very large almost full thickness tears; and that PTRCTs would be usually treated with non-operative treatment. MSAC noted for FTRCTs, there was an upcoming Australian Rotator Cuff (ARC) trial: multicentre placebo-controlled RCT of repair for full thickness supraspinatus tears *vs.* placebo. MSAC considered that it might be informative to see these results and then consider the need and design of research studies which could be referred to the Medical Research Future Fund (MRFF).

## 4. Background

This is the first submission of REGENETEN bioinductive implant for patients with symptomatic PTRCT or FTRCT. MSAC has not previously considered this application.

The PLAC considered this application in December 2018. The PLAC noted that this device is a high cost option for treatment of rotator cuff tear, and referred the application to the MSAC

[2] Karjalainen TV, Jain NB, Page CM, Lähdeoja TA, Johnston RV, Salamh P, Kavaja L, Ardern CL, Agarwal A, Vandvik PO, Buchbinder R. Subacromial decompression surgery for rotator cuff disease. Cochrane Database of Systematic Reviews. 2019(1).

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

for a health technology assessment to determine the comparative clinical and cost effectiveness of the device for listing on the Prostheses List.

The REGENETEN bioinductive implant is not currently funded or reimbursed in the private or public setting.

## 5. Prerequisites to implementation of any funding advice

At the time of application lodgement, REGENETEN was not included on the Australian Register of Therapeutic Goods (ARTG). The REGENETEN collagen implant is a Class III medical device. An application for REGENETEN (Class III medical device) was submitted to the Therapeutic Goods Administration (TGA) on 31 August 2018 (Application Number DV-2018-CA-16564-1).

The proposed TGA indication is for the management and protection of rotator cuff tendon injuries in which there has been no substantial loss of tendon tissue.

In the pre-MSAC response, the applicant indicated that that the REGENETEN implant has received a positive TGA Conformity Assessment and that inclusion of REGENETEN in the ARTG is expected by the end of July 2020.

The applicant stated that, to date, REGENETEN has only been used in Australia through the TGA Special Access Scheme (SAS).

## 6. Proposal for public funding

The ADAR stated that this application is for a Prostheses List listing of REGENETEN for use in the surgical repair of rotator cuff tears in conjunction with existing MBS items (48960[4], 48906 and 48909). This application does not seek a new MBS item number or to amend an existing MBS item number.

The Commentary noted that these MBS items do not include restrictions associated with clinical indications (e.g. partial versus full thickness rotator cuff tear; symptomatic versus asymptomatic, degenerative tears versus acute trauma) or prior interventions (e.g. previous repair of rotator cuff). These MBS items are therefore unable to restrict access to REGENETEN according to the ADARs proposed population. In the pre-ESC response, the applicant highlighted that it was accepted by PLAC, agreed to by PASC as reflected in the Ratified PICO and acknowledged by the Commentary that the current MBS items are relevant, clinically appropriate and "suitable for this procedure"; allowing the use of REGENETEN in PTRCT and FTRCT patients when the product obtains listing on the Prostheses List (PL).

The ADAR stated that REGENETEN is considered to be a 'once-only' procedure per tendon. The Commentary considered it was unclear how this restriction could be implemented or monitored in practice. Should the proposed device be listed on the Prostheses List, the relevant authorities may wish to consider introduction of measures to implement the once-only per shoulder restriction, for example in the form of maximum life-time limit for orthodontic benefits by private health providers. In the pre-ESC response, the applicant highlighted that consistent with Australian Expert Clinical advice and with the Ratified PICO, evidence from the current Australian REGENETEN TGA SAS program show that all of the **redacted** patients to date received just the one single implant which demonstrates that

[4] The ADAR stated of these, MBS item 48960 is the most applicable item given it refers to arthroscopic repair.

REGENETEN is used only once per tendon in all patients. The applicant considered this is also supported by (i) the data collected the currently running USPMCF study (n=138; 33 PTRCT, 115 FTRCT); and (ii) real-world-evidence from a retrospective analysis of the Premier database (a USA hospital discharge data from more than 400 hospitals) from January 2018 to September 2019.

## 7. Summary of public consultation feedback/consumer Issues

Nil.

## 8. Proposed intervention's place in clinical management

**Description of Proposed Intervention**

The proposed medical service is surgical repair of rotator cuff tear including a bovine bioinductive collagen implant. The REGENETEN bioinductive implant is a bioabsorbable implant device that provides a layer of collagen over injured tendons, intended to induce new host tissue growth.

**Description of Medical Condition(s)**

Prevalence of rotator cuff abnormalities rises steeply with increasing age, from 9.7% in patients aged ≤20 years to 62% in patients aged ≥80 years. The incidence of rotator cuff tears ranges from 5% to 40%. However, since not all rotator cuff tears are symptomatic, the true incidence is difficult to determine. The ADAR, quoting Sher (1995)[5], reported that partial-thickness tears are two to three times more likely to occur, and are often much more painful, than full-thickness tears. The risk of tear progression correlates with percentage tendon thickness at presentation: progression has been observed in 55% of patients with ≥50% tearing of tendon thickness at presentation compared to 14% of patients with <50% tearing[6]. Progression of symptomatic PTRCTs to FTRCTs with non-operative treatment has been seen in 18% of patients followed up for over 1 year, with a further 34% exhibiting increase in partial tear size.[7]

The intended population is patients who have symptomatic rotator cuff tears of the shoulder. There are two subpopulations, grouped by depth of the rotator cuff tear:

- Subpopulation 1: patients with symptomatic partial-thickness rotator cuff tear (PTRCT) who have failed at least three months of conservative (non-surgical) management and are considered eligible for (or indicated for) surgical repair
- Subpopulation 2: patients with symptomatic full-thickness rotator cuff tear (FTRCT) who have failed at least three months of conservative (non-surgical) management and are considered eligible for (or indicated for) surgical repair.

The ADAR estimated prevalence of PTRCTS was 71% and FTRCTs was 29% from Sher (1995). In the pre-MSAC response, the applicant provided Australian estimates of prevalence rates of PTRCT and FTRCT (Table 1).

[5] Sher, J. S., J. W. Uribe, A. Posada, B. J. Murphy and M. B. Zlatkin (1995). "Abnormal findings on magnetic resonance images of asymptomatic shoulders." J Bone Joint Surg Am 77(1): 10-15.
[6] Denkers, M., K. Pletsch and R. Boorman (2012). Partial thickness rotator cuff tears: observe or operative. . Proceedings of the American Academy of Orthopaedic Surgeons Annual Meeting. San Francisco, Calif, USA.
[7] Yamanaka, K. and H. Fukuda (1987). " Pathological studies of the supraspinatus tendon with reference to incomplete thickness tear." Katakansetsu 11(1): 98-102. .

**Table 1: Australian Prevalence rates of PTRCT and FTRCT**

| Reference | Setting (dates, location) | Rotator cuff surgery population | PTRCT | FTRCT |
|---|---|---|---|---|
| Yeo 2017 | Australia<br>Aug 2005- Dec 2012<br>Orthopaedic Research Institute, St. George Hospital Campus, NSW | N=1,624<br>Retrospective cohort study of patients who underwent arthroscopic rotator cuff repair | 626 (39%) | 998 (61%) |
| Elkins 2019 | Australia<br>May 2005- May 2016<br>Orthopaedic Research Institute, St. George Hospital Campus, NSW | N=1,000<br>Retrospective analysis of prospectively collected data in patients undergoing arthroscopic rotator cuff repair by the under-surface repair technique | 478 (48%) | 522 (52%) |
| McColl 2019 | Australia<br>Oct 2005- Oct 2013<br>Orthopaedic Research Institute, St. George Hospital Campus, NSW | N=1471 (1,600*)<br>Retrospective cohort study of patients who underwent arthroscopic rotator cuff repair | 660 (45%) | 811 (55%) |
| Klironomos 2020 | Australia<br>Feb 2004 – Dec 2015<br>Orthopaedic Research Institute, St. George Hospital Campus, NSW | N=1,747<br>Retrospective cohort study of patients who was diagnosed with rotator cuff tear | 721 (41%) | 1,026 (59%) |

Source: Table 1, p6 of applicant pre-MSAC response
N, number of patients. Notes: * 129 (8%) of patients, tear thickness was not recorded

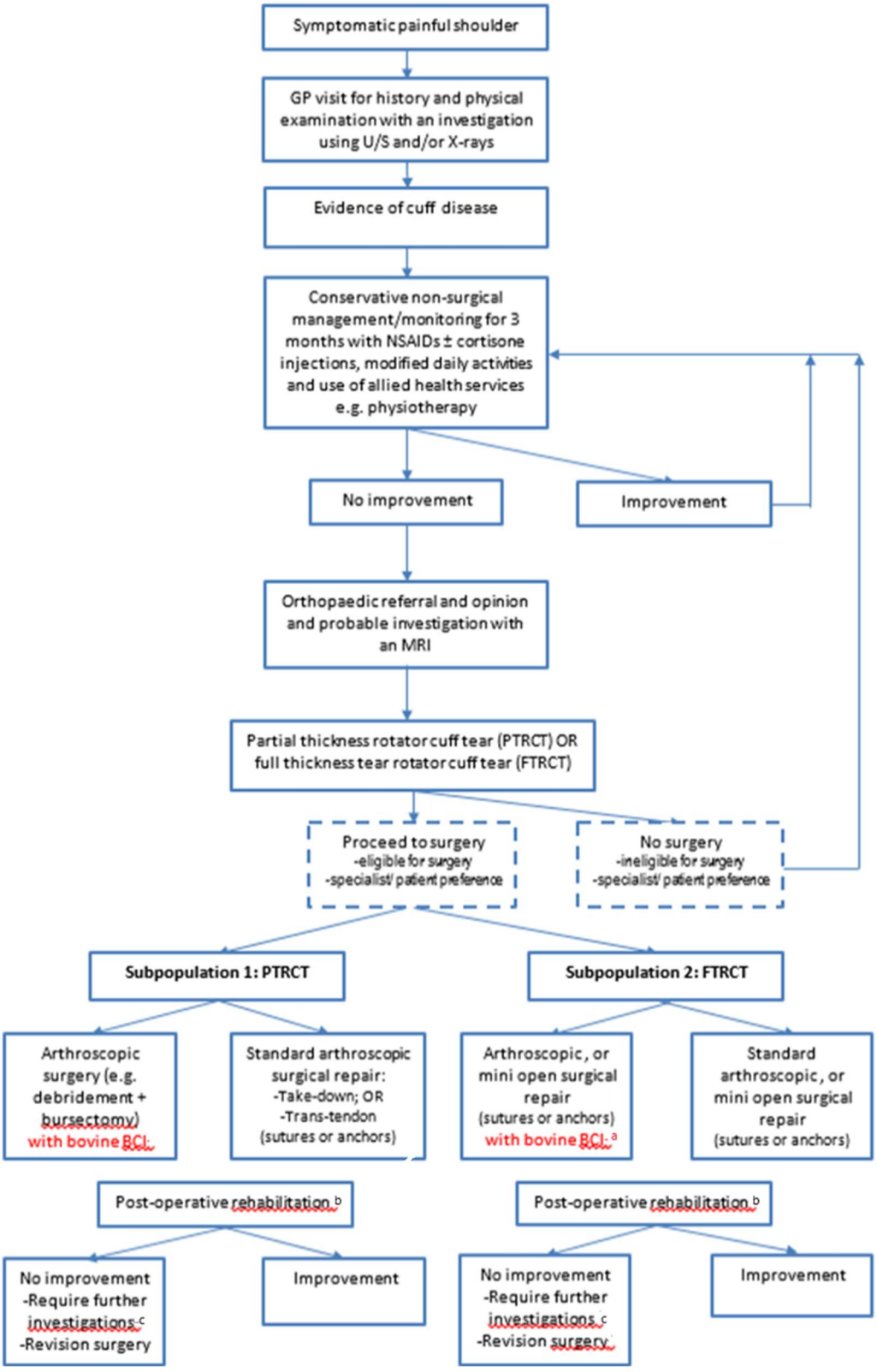
## Place in clinical management

The applicant's current and proposed clinical management algorithms (Figure 1) are based on consultation with experts as there are no Australian-specific guidelines. The treatment algorithm proposes that REGENETEN is an alternative to surgical repair for patients with PTRCTs and in addition to surgical repair for patients with FTRCTs.

The Commentary noted there were some minor differences regarding the removal of footnotes in the ADARs algorithm compared with the Ratified PICO confirmation's algorithm, which noted:

- one patient in Bokor (2015) received REGENETEN following a take-down repair of PTRCT. The Commentary stated that this is not consistent with the application's claim that REGENETEN will replace surgical repair of PTRCTs. In the pre-ESC response, the applicant recalled PASC accepted that the Bokor 2015 study was an early feasibility study investigating use of REGENETEN in patients with FTRCTs (*not PTRCTs*) and the one patient mentioned in the Commentary had a high-grade PT tear which was converted to FTRCT before repair with REGENETEN following the treatment algorithm of FTRCTs. Thus, the applicant considered that the surgical technique used in this study/patient does not represent the management algorithm currently being used in patients with PTRCTs. Furthermore, the applicant considered use of REGENETEN as an alternative treatment option to standard surgical repair in symptomatic PTRCTs (subpopulation 1) is supported by the body of evidence provided in the ADAR and by the use of REGENETEN in the **redacted** patients to date in the current Australian TGA SAS program
- Two patients in Thon (2019) with FTRCTs experienced clinical failure. One of these patients received revision surgery. This is not considered in the ADARs economic model which assumed that revision surgery to be equal to the re-tear rate.

**Figure 1 Current and proposed treatment algorithms for subpopulations 1 and 2 in the ADAR**




*Source: Figure 8, p46 of the ADAR*

*BCI = bioinductive collagen implant, FTRCT = full thickness rotator cuff tear, MRI = magnetic resonance imaging, MRA = magnetic resonance arthrography, NSAID = non-steroidal anti-inflammatory drugs, PTRCT = partial thickness rotator cuff tear, U/S = ultrasound*

*a All patients with FTRCTs in Bokor 2015 and Thon 2019 received bovine BCI after surgical repair (sutures or anchors)*

*b After receiving surgery patients are followed up for 3 months as routine practice*

*c Possible investigations could include MRI, physical therapy sessions, and treatments for pain management*

## 9. Comparator

The proposed comparator for REGENETEN in both patient subpopulations is standard surgical repair. For PTRCTs, REGENETEN is applied instead of standard surgical repair with sutures or anchors; for FTRCTs, REGENETEN is applied in addition to standard surgical repair.

Standard surgical repair in patients with PTRCTs includes debridement, diagnosis and bursectomy; followed by surgical repair of the tendon using a trans-tendon or take-down technique. Trans-tendon repair involves maintaining the intact lateral portion of the tendon while repairing the medial aspect of the tendon. Take-down repair involves artificially completing the tear during the surgery followed by standard rotator cuff repair using anchors and sutures.

Standard surgical repair in patients with FTRCTs includes debridement, diagnosis and bursectomy; followed by reattaching the muscle to the bone using anchors and sutures.

The Commentary stated that the comparators are appropriate and consistent with the ratified PICO confirmation. The comparators are hospital based – when performed in the private setting they are associated with MBS item numbers (48960, 48906 and 48909).

## 10. Comparative safety

The ADAR reported that there were no direct randomised trials comparing REGENETEN versus standard surgery in patients with partial or full-thickness rotator cuff tear, nor comparative studies that involved REGENETEN. Thus, the ADAR relied on *naïve* indirect comparisons to derive estimates of the comparative effectiveness and safety of REGENETEN versus standard surgery in both subpopulations (Table 2).

**Table 2 Overview of the evidence base presented in the ADAR**

| | Subpopulation 1 (PTRCT) | | Subpopulation 2 (FTRCT) | | Total | |
|---|---|---|---|---|---|---|
| | REGENETEN | Standard Surgery | REGENETEN | Standard Surgery | REGENETEN | Standard Surgery |
| Number of treatment arms / number of studies included | 3 / 3 | 7 / 5 | 3 / 3 | 62 / 42 | 6 / 5 | 69 / 45 |
| Study design = RCT | 0 | 5 / 3 | 0 | 41 / 27 | 0 | 46 / 29 |
| Study design = NRCS | 0 | 1 / 1 | 0 | 11 / 6 | 0 | 12 / 6 |
| Study design = CS | 3 / 3 | 1 / 1 | 3 / 3 | 10 / 9 | 6 / 5 | 11 / 10 |
| Total number of study participants | 136 | 325* | 115 | 2,884* | 251 | 3,209* |
| Key outcome measures used to support claim of superiority in comparative effectiveness | | | | | | |
| | Total number of study participants / Number of treatment arms | | | | | |
| Re-tear (Imaging outcome) | 136 / 3 | 141 / 4 | 115 / 3 | 1,852^ / 46 | | |
| Incomplete healing (Imaging outcome) | 136 / 3 | 201 / 6 | 115 / 3 | 1,965^ / 47 | | |
| Treatment failure (Imaging outcome) | 136 / 3 | 201 / 6 | 115 / 3 | 2,256^ / 53 | | |
| Key outcome measures used to support claim of non-inferiority in comparative safety | | | | | | |
| | Total number of study participants / Number of treatment arms | | | | | |
| Revision surgery | 136 / 3 | 64 / 1 | 115 / 3 | 912 / 19 | | |

*ADAR=Applicant Developed Assessment Report; CS=case series; FTRCT=full-thickness rotator cuff tear; NRCS=non-randomised comparative studies; PTRCT=partial-thickness rotator cuff tear; RCT=randomised controlled trial*
*Note that this table was not provided in the ADAR but was constructed during the evaluation. While the numbers of participants for REGENETEN studies reported here were consistent with the main body of the ADAR and the spreadsheet provided in Appendix 13, the numbers of participants for the standard surgery studies are not. The number of participants for standard surgery for the different outcomes were computed based on the relevant spreadsheets supplied in Appendix 13. Where there are discrepancies between the main body and Appendix 13 of the ADAR, data from Appendix 13 are presented here.*
** These numbers referred to the total number of study participants enrolled or randomized in the treatment arms.*
*^ These numbers referred to the total number of patients with follow-up scans.*
*Source: Tables 21-24, pp61-67 of the ADAR; Appendix 13 of the ADAR*

The ADAR identified five REGENETEN studies (all open prospective observational studies): two in PTRCT (Bokor 2016[8], n=13; Schlegel 2018[9], n=33), two in FTRCT (Bokor 2015[10], n=9; Thon 2019[11], n=23) and one in both (McIntyre 2019[12]; PTRCT: n=90; FTRCT: n=83). Bokor 2015, 2016 were Australian studies. The other three were US studies. The

[8] Bokor, D. J., D. Sonnabend, L. Deady, B. Cass, A. Young, C. Van Kampen and S. Arnoczky (2016). "Evidence of healing of partial-thickness rotator cuff tears following arthroscopic augmentation with a collagen implant: a 2-year MRI follow-up." Muscles Ligaments Tendons J 6(1): 16-25.
[9] Schlegel, T. F., J. S. Abrams, B. D. Bushnell, J. L. Brock and C. P. Ho (2018). "Radiologic and clinical evaluation of a bioabsorbable collagen implant to treat partial-thickness tears: a prospective multicenter study." Journal of Shoulder and Elbow Surgery 27(2): 242-251.
[10] Bokor, D. J., D. Sonnabend, L. Deady, B. Cass, A. Young, C. Van Kampen and S. Arnoczky (2015). "Preliminary investigation of a biological augmentation of rotator cuff repairs using a collagen implant: a 2-year MRI follow-up." Muscles Ligaments Tendons J 5(3): 144-150.
[11] Thon, S. G., L. O'Malley, M. J. O'Brien and F. H. Savoie (2019). "Evaluation of Healing Rates and Safety With a Bioinductive Collagen Patch for Large and Massive Rotator Cuff Tears: 2-Year Safety and Clinical Outcomes." The American journal of sports medicine 47(8): 1901-1908.
[12] McIntyre, L. F., B. D. Bushnell, S. W. Trenhaile and P. B. Brown (2018). "Partial and Full Thickness Rotator Cuff Repair with Bioinductive Implants." Arthroscopy - Journal of Arthroscopic and Related Surgery 34(12): e5.

Commentary stated that the non-randomised data for REGENETEN, which the majority had sample sizes <30, had a high risk of bias, including selection bias.

Forty-five studies for standard surgery were included, which the majority (64.4%) were randomised controlled trials (RCTs): five studies (n=325) in PTRCT and 42 (n=2,884) in FTRCT. The ADAR stated study duration ranged between 12 and 60 months with majority of studies following patients between 12 and 24 months.

The ADAR performed meta-analyses for REGENETEN and standard surgery studies within each population. The ADAR stated that variation in the definition of outcomes, amount of follow-up and study design meant there was potential for a large degree of heterogeneity in the meta-analyses. Accordingly, the random effects models were used to produce pooled estimates of treatment effect. Due to the limitations of comparing single arm studies, it was not possible to compute, and, thus compare, relative risks. The Commentary stated that the indirect comparisons conducted were naïve, not via a common comparator as described by Bucher et al. 1997[13]. The relative effectiveness estimates presented were not adjusted via any common comparator between REGENETEN and standard surgery.

The ADAR stated that patients' characteristics were well matched between the studies of REGENETEN and standard surgery in terms of age, gender and type of tear. The ADAR did note one key difference was that for some patients enrolled in the REGENETEN studies, the index procedure was a revision surgery, whereas revision surgeries were generally excluded in standard surgery studies. As revision surgeries are more prone to failure, this may bias the comparative clinical analysis against REGENETEN.

However, the Commentary considered that the studies of standard surgery were highly heterogeneous, especially for subpopulation 2 (FTRCT):

- For both subpopulations, comparability of the patient population across the studies of standard surgery versus the REGENETEN studies at baseline was not clear. The ADAR only addressed the issue in terms of age and gender distribution in Section C.2. However, baseline patient population comparability should also include disease characteristics (e.g. tear location, extent, tear size) and co-existing shoulder pathology, as these might impact on the index surgical techniques and concomitant procedures performed, thereby impacting on effectiveness. Study-level information on these characteristics were not provided in the ADAR. Comparability of the REGENETEN and standard surgery studies were therefore unclear.
- For both subpopulations, comparability of the surgical intervention performed across the standard surgery studies versus the REGENETEN studies was also not clear. A wide variety of surgical procedures were performed across the standard surgery studies some of which may not be applicable to current practice, as most standard surgery studies were conducted 10-15 years ago. In addition, some studies included trauma repair, not included in the proposed use. Thus, there were applicability concerns with the comparator studies included in the naïve comparison.

*Procedural complications and long-term adverse events*
The ADAR reported that there were no long-term adverse events (AEs) across all REGENETEN studies (Table 3).

[13] Bucher, HC, Guyatt, GH, Griffith, LE & Walter, SD. 1997. 'The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials', J Clin Epidemiol, vol. 50, no. 6, Jun, pp. 683-691.

**Table 3 Summary of results of procedural complications**

| | REGENETEN | Standard Surgery |
|---|---|---|
| Subpopulation 1 (PTRCT) | | |
| Event rate in individual studies, range (%) | 0% (0/13-90) - 9.1% (3/33) | 0% (0/12-64) - 7.1% (2/29) |
| Events | Cardiac ablation, allergic skin reaction, wound drainage due to a stitch abscess | Adhesive capsulitis |
| Subpopulation 2 (FTRCT) | | |
| Event rate in individual studies, range (%) | 0% (0/23) - 3.6% (3/83) | 0% (0/14-108) - 4.3% (2/47) |
| Events | Postoperative infection, DVT, graft remains and loosened in bursa at 4 months post-surgery | NR |

*DVT=deep vein thrombosis; FTRCT=full-thickness rotator cuff tear; PTRCT=partial-thickness rotator cuff tear*
*Source: Table 5, pxv of the Commentary*

The Commentary considered long-term AEs for REGENETEN was limited to 11 patients with PTRCT at five years follow-up in Bokor 2019[14], the follow-up study for Bokor 2016. There is no long-term AE data for the use of REGENETEN in patients with FTRCT. The ADAR did not report on long-term AEs across the studies for standard surgery.

*Revision surgery*
For PTRCT (subpopulation 1), all three REGENETEN case series reported rates of revision surgery, with the event rate ranging from 1.1% (1/90 in McIntyre 2019) to 15.4% (2/13 in Bokor 2016). Only one study (Peter 2012) of standard surgery reported on revision surgery, which five patients (7.8%) in the PTRCT arm (N=64) of the study had revision surgery. The Commentary noted that revision surgery rate in Peters 2012 was assessed at 24 months post-surgery whereas the revision surgery rates in the REGENETEN studies ranged from 12 to 27 months (Table 102 in Attachment B). If only rates at 24 months are considered, the revision surgery rate for standard surgery appears to be lower (7.8% in Peters 2012), compared to REGENETEN (15.4% in Bokor 2016) [see Table 4 below].

For FTRCT (subpopulation 2), all three REGENETEN case series reported on revision surgery, with the event rate ranging from 0% (0/9) in Bokor 2015, to 4.35% (1/23) in Thon 2019 and 8.4% (7/83) in McIntyre 2019. Thirteen studies (19 treatment arms) of standard surgery reported on revision surgery, with the event rate ranging from 0% in four treatment arms, to 9.3% (4/43) in Abrams 2014-no acromioplasty. Altogether there were 37 cases of revision surgery in the 19 treatment arms (912 patients in total) [see Table 4 below].

[14] Bokor, D. J., D. H. Sonnabend, L. Deady, B. Cass, A. A. Young, C. L. Van Kampen and S. P. Arnoczky (2019). "Healing of partial-thickness rotator cuff tears following arthroscopic augmentation with a highly-porous collagen implant: a 5-year clinical and MRI follow-up." Muscles, Ligaments and Tendons Journal 9(3): 338-347.

**Table 4 Revision surgery (REGENETEN vs. standard surgery)**

| | REGENETEN | Standard surgery | Difference* |
|---|---|---|---|
| PTRCT (Subpopulation 1) | | | |
| Across treatment arms: range^ / N / n | 1.1%-15.4% / 136 / 3 | 7.8% / 64 / 1 | – |
| Pooled risk (RE) (95% CI) | 0.018 (−0.011, 0.047), p=0.231, Q = 2.31 (df=2), $I^2$ = 0.14 | **0.078 (0.012, 0.144)**, p<0.001, df=0 | −0.060 (−0.132, 0.012), p=0.050 |
| FTRCT (Subpopulation 2) | | | |
| Across treatment arms: range^ / N / n | 0-8.4% / 115 / 3 | 0-9.3% / 912 / 19 | – |
| Pooled risk (RE) (95% CI) | **0.069 (0.043, 0.095),** p<0.001, Q=0.64 (df=2), $I^2$=0 | **0.027 (0.017, 0.038**), p-value <0.001, Q=15.14 (df=18), $I^2$=0 | **0.042 (0.014, 0.070)**, p=0.002 |

CI=confidence interval; df=degree of freedom; N=total number of study participants across treatment arms; n=number of treatment arms contributing data; PTRCT=partial-thickness rotator cuff tear; RE=random effects
^ Range (minimum, maximum) of event rates across studies
* Difference (naïve indirect estimate) = REGENETEN − Standard Surgery
Numbers in **bold** represent results that reached statistical significance.
Source: Compiled from Table 31, p28; and Table 41, p43 of the Commentary

## 11. Comparative effectiveness

*Functional and quality of life outcomes*
The ADAR stated that the studies of REGENETEN, for both PTRCT and FTRCT, reported statistically significant improvements from baseline in ASES and Constant-Murley (CM) scores. These improvements exceeded the minimal clinically important differences (MCID) of 11.1 (Cvetanovich 2019[15]) and 20.9 (Tashjian 2017[16]) for the ASES; and after 12 months was greater than twice the MCID of 10.4 (Kukkonen et al 2013[17]) for the CM scores. McIntyre 2019 reported significant and clinically meaningful improvements in the Western Ontario Rotator Cuff (WORC) and visual analogue scale (VAS) pain scales at 12 months.

The ADAR stated that there are no statistically significant differences between REGENETEN and conventional surgery for any patient-reported outcomes over 12-24 months follow-up (Table 4). The Commentary considered there appeared a trend of greater improvement with standard surgery in ASES and Constant-Murley scores for PTRCT and Constant-Murley and WORC scores for FTRCT, when compared with REGENETEN, although the difference did not reach statistical significance (Table 5).

The Commentary stated no naïve comparison was possible for assessing rehabilitation outcomes due to no evidence for standard surgery.

[15] 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." J Shoulder Elbow Surg 28(5): 939-948.
[16] Tashjian, R. Z., J. Deloach, C. A. Porucznik and A. P. Powell (2009). "Minimal clinically important differences (MCID) and patient acceptable symptomatic state (PASS) for visual analog scales (VAS) measuring pain in patients treated for rotator cuff disease." J Shoulder Elbow Surg 18(6): 927-932.
[17] Kukkonen, J., A. Joukainen, J. Lehtinen, K. T. Mattila, E. K. Tuominen, T. Kauko and V. Aarimaa (2014). "Treatment of non-traumatic rotator cuff tears: A randomised controlled trial with one-year clinical results." Bone Joint J 96-B(1): 75-81.

**Table 5 Naïve indirect comparison of patient-reported outcomes between REGENETEN and standard surgery**

| Functional outcomes | Pooled risk (RE) (95% CI) | | Difference* |
|---|---|---|---|
| | REGENETEN | Standard surgery | |
| PTRCT | | | |
| ASES Score | 34.57 (28.39, 40.75)<br>p<0.001, Q=0.20 (df=1), $I^2$=0 | 40.52 (35.68, 45.36)<br>p<0.001, Q=114.78 (df=5), $I^2$=0.96 | −5.95 (−13.80, 1.90)<br>p=0.07 |
| Constant-Murley Score | 24.30 (11.15, 37.45) | 36.37 (20.28, 52.46)<br>p<0.001, Q = 38.69 (df=2), $I^2$ = 0.95 | −12.07 (−32.85, 8.71),<br>p=0.13 |
| VAS Pain Score | NR | NR | − |
| WORC Score | NR | NR | − |
| FTRCT | | | |
| ASES Score | 41.27 (36.82, 45.71),<br>p<0.001, Q = 0.11 (df=1), $I^2$ = 0 | 40.87 (38.23, 43.51),<br>p<0.001, Q = 1706.8 (df=30), $I^2$ = 0.98 | 0.40 (−4.77, 5.56),<br>p=0.44[a] |
| Constant-Murley Score | 27.30 (16.69, 37.91) | 32.45 (29.14, 35.75)<br>p<0.001, Q = 605.88 (df=38), $I^2$ = 0.94 | −5.15 (−16.26, 5.97)<br>p=0.18[b] |
| VAS Pain Score | −4.34 (−6.30, −1.70) | −4.34 (−4.90, −3.78); p <0.001;<br>Q=1422, df=32, $I^2$ = 0.98 | 0.34 (−2.02, 2.70),<br>p=0.61 |
| WORC Score | 45.10 (19.24, 70.96) | 53.49 (50.42, 56.57), p=0.26, Q = 1.80 (df=4), $I^2$ = 0 | −8.39 (−34.35, 17.56),<br>p=0.26 |

*ASES=American Shoulder and Elbow Surgeons; CI=confidence interval; ; df=degree of freedom; $I^2$ statistic; FTRCT=full-thickness rotator cuff tear; NR=not reported; PTRCT=partial-thickness rotator cuff tear; Q=Chi-square for heterogeneity; RE=random effects; WORC=Western Ontario Rotator Cuff*

** Difference (naïve indirect estimate) = REGENETEN − Standard Surgery*

*[a] The 95% CI of the difference did not reach the MCID based on Cvetanovich 2019 or Tashjian 2017.*

*[b] The 95% CI of the difference did not reach the MCID based on Kukkonen 2013.*

*Source: Table 7, pxvi of the Commentary*

*Imaging outcomes*

The ADAR stated that there was considerable heterogeneity in the reporting and classification of imaging outcomes. To make best use of the available data, three imaging outcomes were defined and synthesised from the available evidence; re-tears[18], incomplete healing[19] and treatment failure. The Commentary presented the results for imaging outcomes that were used in the economic evaluation (Table 6).

[18] The term re-tear was defined for this analysis as a full thickness defect in the index shoulder during follow-up diagnosed using magnetic resonance imaging (MRI) or ultrasound imaging (US)

[19] The term "incomplete healing" defined as a failure to achieve full thickness in all repaired tendons (partial and full thickness defects observed in follow-up). This included mentions in the literature of re-tear and healing rates. It also included Sugaya type III, IV and V tears, and intermediate and high grade defects defined by the Ellman classification

**Table 6 Overview of results of key effectiveness outcomes**

| | REGENETEN (95% CI) | Standard Surgery (95% CI) | Difference (=REGENETEN − Standard Surgery) (95% CI) |
|---|---|---|---|
| Subpopulation 1 (PTRCT) | | | |
| Imaging outcomes | Pooled risk | Pooled risk | Difference |
| Incomplete Healing | 0.049 (−0.028, 0.126) | **0.060 (0.032, 0.089)^** | −0.011 (−0.093, 0.071) |
| Re-tears | 0.008 (−0.003, 0.018) | **0.090 (0.062, 0.117)** | **−0.082 (−0.111, −0.053)** |
| Subpopulation 2 (FTRCT) | | | |
| Imaging outcomes | Pooled risk | Pooled risk | Difference |
| Incomplete Healing | **0.048 (0.044, 0.052)** | **0.247 (0.197, 0.298)** | **−0.200 (−0.250, −0.149)** |
| Re-tears | **0.033 (0.021, 0.044)** | **0.177 (0.134, 0.219)** | **−0.144 (−0.188, −0.100)** |

ADAR=Applicant Developed Assessment Report; ASES=American Shoulder and Elbow Surgeons; CI=confidence interval; FTRCT=full-thickness rotator cuff tear; NNT=number needed to treat; NNH=number needed to harm; PTRCT=partial-thickness rotator cuff tear; VAS=Visual Analogue Scale; WORC=Western Ontario Rotator Cuff

^ Note that the same studies contributed the same event data to the outcome measures of treatment failure and incomplete healing for standard surgery (PTRCT), hence the same pooled estimates for both outcomes.

Numbers in **bold** represent results that reached statistical significance.

Numbers in red were used in Section D of the ADAR.

*Source: Tables 35-39, 42-52 and 54-58, pp96-101 and 105-128 of the ADAR; Excel Workbook 'Appendix 13 Synthesis of Evidence', included in electronic Appendix folder of the ADAR.*

## Clinical claim

Based on the evidence provided in Section B for both patient subpopulations, the ADARs comparative clinical claim for REGENETEN versus standard surgical repair (i.e. without use of REGENETEN) is superior effectiveness for functional outcomes and non-inferior safety. However, the Commentary raised the following concerns:

- For subpopulation 1 (PTRCT), the adequacy of the evidence provided to support the claim of non-inferiority in comparative safety of REGENETEN versus standard surgery is unclear given the lack of direct comparative data of REGENETEN versus standard surgery and the scarcity of long-term safety data (limited to 11 patients followed at 5 years after the index procedure in Bokor 2019)
- For subpopulation 2 (FTRCT), claim of non-inferiority in comparative safety of REGENETEN versus standard surgery in subpopulation 2 (FTRCT) is not supported by the statistically significantly higher revision surgery rates with REGENETEN; and lack of long-term safety data for REGENETEN beyond two years
- For both subpopulations 1 (PTRCT) and 2 (FTRCT), the claim of superiority in clinical effectiveness was based on statistically significant greater benefit in imaging outcomes, rather than in clinical or patient-relevant outcomes (e.g. functional outcomes, quality of life outcomes) the results of which were not statistically significant. In addition, the method used to derive the 'statistically significantly greater benefit' in imaging outcomes with REGENETEN was based on naïve indirect comparison analyses at high risk of bias, not the Bucher method (Bucher 1997) as claimed in the ADAR. Overall, the claim of clinical superiority has not been supported by the evidence provided.

In the pre-ESC response, the applicant highlighted for comparative safety that:

- the higher revision surgery rates with REGENETEN in the FTRCT subpopulation was essentially driven by the majority of REGENETEN evidence in this subpopulation coming from the USA REBUILD "data registry study" (McIntyre 2019), noting the highly medico-legal environment in USA.
- the naïve comparison is further compounded and biased against REGENETEN by the fact that there appears to be a publication bias among studies of standard surgery with

regards of revision surgery. Twenty one of 32 standard surgery studies of FTRCTs that reported re-tears did not report revision surgeries. The applicant considered it can be reasonably assumed that there should have been some revision surgeries.

- global post market surveillance of **redacted** REGENETEN implants showed 4 (0.01%) reportable complaints (i.e. those reported to a "competent authority" of any country as an adverse event or reportable device malfunction) and 44 (0.14%) total complaints in the close to 5 years period from January 2014 to November 2019. The applicant considered this is far lower than the 0.6% (10/1677) patients in the trials of standard surgery that experienced procedural complications.

In the pre-ESC response, the applicant highlighted for comparative effectiveness that:

- the imaging outcomes were chosen as the primary outcome measure as imaging outcomes are objective outcome measures and directly measure the impact of rotator cuff repair intervention, and MRI is standard care.
- the functional outcomes (CM and ASES scores) are highly sensitive to differences in age, sex and physical strength (Yian 2005[20], Booker 2015). As such they are sensitive to differences in baseline characteristics. The heterogeneous mixture of these characteristics in the available evidence and the limited reporting of these subjective outcome measures in the literature means that the CM and ASES scores are not well suited comparing the two treatments.
- The studies/evidence were powered to detect significant differences in the imaging outcomes. The available studies were not powered to detect differences in clinical or patient relevant outcomes.

*Translation issues*

Two translation issues were addressed in the ADAR:

a) the applicability of the published studies in Section B to the Australian patient population; the Commentary considered this was not adequately addressed as the ADAR only addressed the issue in terms of age and gender distribution but not in terms of tear characteristics (e.g. location of tear, extent of tear, tear size) or concomitant shoulder procedures. In addition, a wide variety of surgical procedures were performed across the standard surgery studies, with study period spanning 2003 to 2016
b) the transformation of re-tear and incomplete healing rates to utility values; The Commentary stated no utility values were reported from the REGENETEN studies and the utility values from a published abstract (Flurry 2019) were used in the ADAR to estimate utilities associated with re-tear and successful surgery in PTRCT and incomplete healing and successful surgery in FTRCT.

## 12. Economic evaluation

The ADARs economic evaluation is summarised in Table 7.

[20] Yian, EH, Ramappa AJ, et al. "The Constant score in normal shoulders." J Shoulder Elbow Surg 2005; 14; 128-133 Yian 2005

**Table 7 Summary of the economic evaluation**

| Perspective | Healthcare payer and societal^ |
|---|---|
| Comparator | Standard surgery |
| Type of economic evaluation | Cost-utility analysis. |
| Sources of evidence | Systematic literature review |
| Time horizon | 2 years |
| Outcomes | Re-tear rate, Incomplete healing rates, |
| Methods used to generate results | Expected value analysis |
| Health states | PTRCT: Re-tear (QALY=0.67), successful surgery (QALY=0.94)<br>FTRCT: Incomplete healing (comprised of full re-tears and partial re-tears) (QALY=0.67), successful surgery (QALY=0.94) |
| Discount rate | 5% after year 1 |
| Software packages used | MS Excel |

*QALY, quality-adjusted life year*
*^The Commentary stated that the societal perspective is not presented in this executive summary as costs should be related to healthcare costs only (p182, 2016 Technical Guidelines for preparing assessment reports for the Medical Services Advisory Committee – Medical Service Type: Therapeutic (Version 2.0). As described in Section D, the societal perspective should be considered a sensitivity analysis.*
*Source: Table 64, p140 of the ADAR*

The ADAR stated it only incorporated parameters where the values differed in a meaningful way between REGENETEN and standard surgery:

1. Surgical equipment, which includes REGENETEN implant, surgical sutures and anchors
2. Operating theatre time for initial surgery; the Commentary stated this was based on applicant feedback provided in the Ratified PICO (p12)
3. Revision surgery costs (based on re-tear rates)*;* this was not considered appropriate and the evaluation provided a re-specified base-case using revision rates provided in Table 3
4. Number of physiotherapy sessions required for rehabilitation; the Commentary stated this was based on the experience of local clinical expert surgeons experienced in using REGENETEN over a few years from the TGA Special Access Scheme program estimating fewer physiotherapy visits for REGENETEN compared with standard surgery. No data was provided in the ADAR to validate this estimate. However, the number of physiotherapy sessions supported by evidence average between 18 (Schlegel 2018) and 20.6 (McIntyre 2019) sessions for PTRCT and 21.5 (McIntyre 2019) sessions for FTRCT. The relevant economic model from the healthcare payer perspective was sensitive to this assumption (see sensitivity analyses in Table 9 and scenario analyses in Table 10).
5. Time required before returning to work (to measure productivity loss associated with societal costs); the Commentary stated this was again based on assumption from local clinical expert surgeons.
6. Patient benefits based on the imaging outcomes of surgery.

There were several key assumptions incorporated in the ADARs model structure:

- The economic evaluation assumed re-tear rates were a proxy for revision surgery for both subpopulations; the Commentary considered this assumption, that all re-tears will result in a revision surgery and that no revision surgeries will be undertaken for reasons other than a re-tear might not be appropriate
- The prevalence of PTRCTS was 71% and FTRCTs was 29% in the pooled incremental cost-effectiveness ratio (ICER); the Commentary considered this estimate was highly uncertain as Sher 1995 was from a US study of asymptomatic shoulders and the number could not be verified.

- For re-tears, the ADAR assumes the entire 2 years spent with pre-op utility. The Commentary considered this was not appropriate (see respecified base-case model in Table 8 and sensitivity analyses in Table 9).

Overall, the Commentary considered that the model structure used is not well justified due to a number of issues with the chosen health states and the ability to accurately reflect utility values for these health states. The relationship between revision surgery, incomplete healing and re-tear rates is not well defined or supported by the evidence. Given this, the Commentary re-specified the base case economic model (see Table 9).

The resulting incremental costs and outcomes as calculated for the intervention and comparator in the model, and using the Sponsor's base case assumptions, and ICER are shown in Table 8.

**Table 8 Results of the economic evaluations**

| Scenario | Incremental Costs | Incremental QALY | ICER |
|---|---|---|---|
| **ADARs values** | | | |
| Healthcare payer perspective | | | |
| **Pooled result (assuming 71% PTRCT and 29% FTRCT)** | **$3,795** | **0.061** | **$62,020** |
| Subpopulation 1: PTRCT | $3,254 | 0.043 | $75,370 |
| Subpopulation 2: FTRCT | $5,120 | 0.105 | $48,619 |
| Societal perspective (healthcare and societal) | | | |
| Pooled result (assuming 71% PTRCT and 29% FTRCT) | -$10,277 | 0.061 | REGENETEN dominates |
| Subpopulation 1: PTRCT | -$13,883 | 0.043 | |
| Subpopulation 2: FTRCT | -$1,448 | 0.105 | |
| **Pre-ESC and Pre-MSAC values** | | | |
| Healthcare payer perspective | | | |
| **Pooled result (assuming 39% PTRCT and 71% FTRCT)** | **-$4,932** | **0.081** | **$54,175** |
| Societal perspective (healthcare and societal) | | | |
| Pooled result (assuming 39% PTRCT and 71% FTRCT) | -$6,298 | 0.081 | REGENETEN dominates |

*QALY, quality adjusted life year. ICER, incremental cost effectiveness ratio.*
*Source: Compiled from Tables 62 and 63, p73 of the Commentary; and Table 2 , p6 of pre-MSAC response*

In the pre-ESC response, the applicant highlighted that:

- the prevalence of symptomatic PTRCT: FTRCT was conservatively based (as the higher the proportion of FTRCT population, the better the pooled ICER) on the Sher paper and aligned with the Ratified PICO. Australian data from a retrospective cohort study of 1,624 patients who underwent arthroscopic rotator cuff repair showed a prevalence of 39% PTRCTs and 61% FTRCT (Yeo 2017[21]). Use of these figures in the economic evaluation would improve the pooled ICER from $62,020 to $54,175. (see Table 8 above).
- the economic analyses conducted from a societal perspective should not be relegated to just another sensitivity analysis (as done by Commentary), but be included as a critical and central element of the economic analyses.

In the pre-MSAC response, the applicant performed a targeted literature search to provide more certainty around the estimate of prevalence, identifying three additional Australian

[21] Yeo, DY, Walton, JR, Lam, P, Murrell, G A. "The Relationship Between Intraoperative Tear Dimensions and Postoperative Pain in 1624 Consecutive Arthroscopic Rotator Cuff Repairs." Am J Sports Med 2017; 45(4): 788-793.

studies which showed similar prevalence rates of PTRCT and FTRCT to Yeo 2017 (see Table 1).

*Evaluator's re-specified base-case model*

During evaluation, the Commentary re-specified the base case ICER was performed as the ADARs base case pooled ICER failed to accurately represent the cost-effectiveness of REGENETEN due to the following two issues:

a) The PTRCT and FTRCT re-tear rates were used as proxies for revision surgery rates which is not appropriate. The Commentary used the revision surgery rates directly from Section B in the re-specified base case
b) Revision surgeries were included as a cost in the model in the first year, which is appropriate. However, the utility value after revision surgery should be increased in the second year for consistency with the costs. Thus, the Commentary assumed a higher utility value for patients undergoing revision surgery in the second year (Table 9).

**Table 9 Commentary's re-specified base case of the economic evaluation (payer perspective)**

| | PTRCT | | | FTRCT | | | |
|---|---|---|---|---|---|---|---|
| **Scenario** | **Incremental Costs** | **Incremental QALY** | **ICER** | **Incremental Costs** | **Incremental QALY** | **ICER** | **Pooled ICER** |
| Base case | $3,254 | 0.043 | $75,370 | $5,120 | 0.105 | $48,619 | $62,020 |
| *A. Use revision surgery rates rather than re-tear rates* | *$3,471* | *0.043* | *$80,394* | *$6,969* | *0.094* | *$66,186* | *$73,303* |
| *B. Adjust utility value for second year after revision surgery to equal value after successful surgery* | *$3,254* | *0.022* | *$146,972* | *$5,120* | *0.068* | *$74,887* | *$106,766* |
| ***A and B Re-specified base case*** | *$3,471* | *0.016* | *$213,407* | *$6,969* | *0.105^* | *$66,442* | *$106,880* |

*QALY, quality adjusted life year. ICER, incremental cost effectiveness ratio.*
*^ See Section D for further discussion and full details of the FTRCT calculation in **Error! Reference source not found.**.*
*Source: Table 11 of the Commentary*

The results of deterministic sensitivity analyses found that modelled results were most sensitive to the utility values, the number of REGENETEN patches used, and the difference in numbers of physiotherapy visits between treatment arms (Table 10). It was noted the Commentary's respecified base case for the pooled ICER decreased to $79,696 per QALY from the healthcare payer perspective, using the applicant's prevalence estimate provided in the pre ESC response (Yeo 2017).

**Table 10 Key drivers of the economic model, base case and re-specified base case (payer perspective)**

| Description | ICER | Base case | *Re-specified base case* |
|---|---|---|---|
| Base case / re-specified base case | Pooled ICER | $62,020 | *$106,880* |
| Subpopulation 1 | PTRCT ICER | $75,370 | *$213,407* |
| Subpopulation 2 | FTRCT ICER | $48,619 | *$66,442* |
| *Prevalence[a], pre-ESC response values: 39% PTRCT; 61% FTRCT, Yeo 2017 (ADAR base case: 71% PTRCT, 29% FTRCT, Sher 1995* | Pooled ICER | $54,175 | *$79,696* |
| | PTRCT ICER | $75,370 | *$213,407* |
| | FTRCT ICER | $48,619 | *$66,442* |
| Use upper limit of CI for pre-operative utility and the lower limit of the post-operative utility value from Flury 2019 (EQ-5D, abstract) | Pooled ICER | $77,885 | *$134,222* |
| | PTRCT ICER | $94,651 | *$268,000* |
| | FTRCT ICER | $61,056 | *$83,438* |
| Use Huang 2017 utility values (from Vitale et al. using HUI from a survey of 87 patients in US hospital over 1 year) | Pooled ICER | $244,565 | *$436,085* |
| | PTRCT ICER | $283,446 | *$411,571* |
| | FTRCT ICER | $201,545 | *$470,236* |
| Set the number of physiotherapy visits to be equal between REGENETEN and the comparator | Pooled ICER | $74,424 | *$124,966* |
| | PTRCT ICER | $92,951 | *$260,074* |
| | FTRCT ICER | $55,827 | *$73,677* |
| Replace the use of the incomplete healing rate with re-tear rate in FTRCT | Pooled ICER | $72,094 | *$166,516* |
| | PTRCT ICER | $75,370 | *$213,407* |
| | FTRCT ICER | $67,526 | *$131,332* |
| Two REGENETEN patches are required^: affecting surgical devices and operating theatre costs | Pooled ICER | $184,556 | *$285,544* |
| | PTRCT ICER | $244,776 | *$663,097* |
| | FTRCT ICER | $124,107 | *$142,222* |

*CI, confidence interval; EQ-5D = EuroQol-5 dimensions scale; ICER, incremental cost effectiveness ratio; HUI = Health Utilities Index*
*^ The number of REGENETEN patches required was included in sensitivity analyses to make explicit the potential impact of the number of REGENETEN patches used on the ICERs, e.g. in patients with bilateral rotator cuff tears or in patients with rotator cuff tears that involve more than one tendon. Three (Bokor 2015, 2016, Schlegel 2018) of the five REGENETEN studies involved supraspinatus tears only but in Thon (2019), at least two tendons (both supraspinatus and infraspinatus) were involved. It is not entirely clear whether more than one REGENETEN patches may be required in certain occasions. As the REGENETEN patch is available in two sizes, it seems reasonable to suppose that one patch may suffice for both supraspinatus and infraspinatus tears but it is not clear as the ADAR stated that the proposed intervention was intended to be used "once per tendon" (p16, ADAR).*
*[a] Calculated by Department using Commentary's respecified spreadsheet*
*Source: compiled from Table 12, pxxii of the Commentary and from Commentary's respecified spreadsheet*

Scenario analysis

The Commentary performed further scenario testing of the assumptions used in the re-specified base case resulting in the pooled ICER increasing to $688,818 ($501,572 for subpopulation 1 [PTRCT] and $1,378,299 for subpopulation 2 [FTRCT]).

**Table 11 Re-specified base-case model results with modification of uncertain assumptions (payer perspective)**

| Scenario | PTRCT ICER | FTRCT ICER | Pooled ICER |
|---|---|---|---|
| Base case | $75,370 | $48,619 | $62,020 |
| Re-specified base case | $213,407 | $66,442 | $106,880 |
| Re-specified base case with FTRCT incomplete healing replaced by re-tear rate (Scenario 1) | $213,407 | $131,332 | $166,516 |
| Re-specified base case with utility values from Huang 2017 (Scenario 2) | $411,571 | $470,236 | $436,085 |
| Re-specified base case with no differential in the number of physiotherapy visits (Scenario 3) | $260,074 | $73,677 | $124,966 |
| **Alternative scenario of re-specified base case**<br>Re-specified base case with Scenarios 1 through 3 | $501,572 | $1,378,299 | $688,818 |
| Re-specified base case with Scenarios 1 and 2 | $411,571 | $1,242,937 | $589,129 |
| Re-specified base case with Scenarios 1 and 3 | $260,074 | $145,634 | $194,693 |
| Re-specified base case with Scenarios 2 and 3 | $501,572 | $521,447 | $509,877 |

QALY, quality adjusted life year. ICER, incremental cost effectiveness ratio.
Source: Table 13, ppxxiii- xxiv of the Commentary

In the pre-ESC response, the applicant:

- noted that the utility scores from Vitale et al using the EuroQol-5 dimensions scale (EQ-5D), are broadly consistent with the other sources. Grobet (2018) reported a 0.22 improvement, Flury (2019) a 0.27 improvement and Huang (2017) reported a 0.2 improvement – all based on EQ-5D scores. The lower reported improvement in utility noted by the Evaluators as referenced in the alternative analysis is derived from the Health Utilities Index (HUI) rating scale and appears to be widely inconsistent with all other studies that report the incremental benefit using the EQ-5D.
- acknowledges that the additional utility in year 2 following revision surgery as noted by the Evaluators is reasonable.

## 13. Financial/budgetary impacts

An epidemiological approach has been used to estimate the financial implications of the introduction of REGENETEN. The financial implications were based on the output from the economic evaluation and the expected utilisation of REGENETEN, assuming the incidence rate from a population-based Finland study (131 rotator cuff repairs per 100,000 population) would remain stable, using the proportion of Australians with private health insurance (44.2%); and the Sponsor's assumption that uptake increasing linearly at **redacted**% per year, reaching **redacted**% in year 5. Consistent with the ADARs economic model, the ADARs base case estimate of prevalence was assuming 71% PTRCT and 29% FTRCT from Sher 2017.

The Commentary re-calculated the ADARs base case costs as per Table 12.

**Table 12 Elements of the costs associated with REGENETEN, as presented in the ADAR vs. Recalculated**

| Costs | ADAR | *Recalculated* |
|---|---|---|
| **Other MBS** | • MBS items 23025, 23045 and 23065 from the initial use of REGENETEN<br>• MBS items 63325 associated with the change in estimated number of revision surgeries | • MBS items 23025, 23045 and 23065 from the initial use of REGENETEN<br>• MBS items 63325 as well as MBS items 17610, 23045, and 48960 associated with the change in estimated number of revision surgeries |
| **Hospital** | • Changes in Operating Theatre time from initial use of REGENETEN<br>• Public payer AR-DRG-I16Z associated with the change in estimated number of revision surgeries | • Changes in Operating Theatre time from initial use of REGENETEN |
| **PHI** | • Reduced number of physiotherapy visits from use of REGENETEN, based on KOL input. Has input error for the number of visits. | • Reduced number of physiotherapy visits from use of REGENETEN, based on KOL input. With number of visits input error corrected.<br>• Private payer AR-DRG-I16Z associated with the change in estimated number of revision surgeries |

*Source: Table 14, pxxv of the Commentary*

The ADARs financial implications to the three payer sources, resulting from the proposed Prostheses List listing of REGENETEN, are summarised in Table 13, noting that the Commentary's recalculated values are presented also in italics below.

**Table 13 Total costs to the MBS with REGENETEN from ADAR- Pooled (prevalence: 71/29% PTRCT/FTRCT)**

| - | 2020 | 2021 | 2022 | 2023 | 2024 |
|---|---|---|---|---|---|
| **REGENETEN** | **-** | **-** | **-** | **-** | **-** |
| Number of services | **redacted** | **redacted** | **redacted** | **redacted** | **redacted** |
| Sub-total direct cost to MBS | $0 | $0 | $0 | $0 | $0 |
| **Revision surgeries and anaesthesia costs for initial surgery** | | | | | |
| Estimated change in services | -29 | -59 | -90 | -122 | -155 |
| Sub-total cost to MBS^ | -$12,534<br>*-$36,064* | -$25,477<br>*-$73,308* | -$38,830<br>*-111,728* | -$52,582<br>*-151,300* | -$66,755<br>*-192,079* |
| **Estimated change in services** | -29 | -59 | -90 | -122 | -155 |
| **Total costs to MBS** | -$12,534<br>*-$36,064* | -$25,477<br>*-$73,308* | -$38,830<br>*-111,728* | -$52,582<br>*-151,300* | -$66,755<br>*-192,079* |
| **Total hospital costs** | -$284,043<br>*-$39,601* | -$577,387<br>*-$80,500* | -$879,984<br>*-$122,688* | -$1,191,657<br>*-$166,141* | -$1,512,844<br>*-$210,922* |
| **Total costs to PHI** | **$redacted**<br>***$redacted*** | **$redacted**<br>***$redacted*** | **$redacted**<br>***$redacted*** | **$redacted**<br>***$redacted*** | **$redacted**<br>***$redacted*** |
| **Total overall cost** | **$redacted**<br>***$redacted*** | **$redacted**<br>***$redacted*** | **$redacted**<br>***$redacted*** | **$redacted**<br>***$redacted*** | **$redacted**<br>***$redacted*** |

*MBS=Medicare Benefits Schedule; Negative costs = savings. Negative services = reduced utilization; PHI=private health insurance*
The ADAR applied the cost of revision surgeries to 'Total hospital costs' using a public AR-DRG-I16Z. The recalculated values apply a private payer AR-DRG- I16Z (as a cost to PHI) and MBS items 17610, 23045 and 48960 as costs to MBS.
Number of services of REGENETEN reflect the expected uptake of REGENETEN and the 'Estimated change in services' reflects changes in revision surgeries, based on the revision surgery rate specified in Table 78 pp155-156 in the ADAR
Source: Table 15, pxv of the Commentary

As per ESC advice, the ADARs financial estimates informing Table 13 have also been presented separately for each subpopulation below (subpopulation 1: Table 14; subpopulation 2; Table 15).

**Table 14 Total costs to the MBS associated with REGENETEN from ADAR- subpopulation 1 (PTRCT; 71%)**

| - | 2020 | 2021 | 2022 | 2023 | 2024 |
|---|---|---|---|---|---|
| **REGENETEN** | - | - | - | - | - |
| Number of services | **redacted** | **redacted** | **redacted** | **redacted** | **redacted** |
| Sub-total direct cost to MBS | $0 | $0 | $0 | $0 | $0 |
| **Revision surgeries and anaesthesia costs for initial surgery** | | | | | |
| Estimated change in services | -17 | -35 | -53 | -71 | -91 |
| Sub-total cost to MBS | -$11,420<br>*-$25,241* | -$23,214<br>*-$51,309* | -$35,380<br>*-$78,199* | -$47,910<br>*-$105,896* | -$60,824<br>*-$134,438* |
| **Estimated change in services** | -17 | -35 | -53 | -71 | -91 |
| **Total costs to MBS** | -$11,420<br>*-$25,241* | -$23,214<br>*-$51,309* | -$35,380<br>*-$78,199* | -$47,910<br>*-$105,896* | -$60,824<br>*-$134,438* |
| **Total hospital costs** | -$209,585<br>*-$66,002* | -$426,034<br>*-$134,166* | -$649,310<br>*-$204,480* | -$879,283<br>*-$276,902* | -$1,116,275<br>*-$351,536* |
| **Total costs to PHI** | **$redacted**<br>***$redacted*** | **$redacted**<br>***$redacted*** | **$redacted**<br>***$redacted*** | **$redacted**<br>***$redacted*** | **$redacted**<br>***$4redacted*** |
| **Total overall cost** | **$redacted**<br>***$redacted*** | **$redacted**<br>***$redacted*** | **$redacted**<br>***$redacted*** | **$redacted**<br>***$redacted*** | **$redacted**<br>***$redacted*** |

*MBS=Medicare Benefits Schedule; Negative costs = savings. Negative services = reduced utilization; PHI=private health insurance*
Values in *italics* are the recalculated values based on the changes shown in Table 10
The ADAR applied the cost of revision surgeries to 'Total hospital costs' using a public AR-DRG-I16Z. The recalculated values apply a private payer AR-DRG- I16Z (as a cost to PHI) and MBS items 17610, 23045 and 48960 as costs to MBS.
Number of services of REGENETEN reflect the expected uptake of REGENETEN and the 'Estimated change in services' reflects changes in revision surgeries, based on the revision surgery rate specified in Table 78 pp155-156 in the ADAR
*Source: Compiled post ESC by Department from Commentary Recalculated spreadsheet*

**Table 15 Total costs to the MBS associated with REGENETEN from ADAR- subpopulation 2 (FTRCT; 29%)**

| - | 2020 | 2021 | 2022 | 2023 | 2024 |
|---|---|---|---|---|---|
| **REGENETEN** | - | - | - | - | - |
| Number of services | **redacted** | **redacted** | **redacted** | **redacted** | **redacted** |
| Sub-total direct cost to MBS | $0 | $0 | $0 | $0 | $0 |
| **Revision surgeries and anaesthesia costs for initial surgery** | | | | | |
| Estimated change in services | -12 | -24 | -37 | -50 | -64 |
| Sub-total cost to MBS | -$1,114<br>*-$10,822* | -$2,264<br>*-$21,999* | -$3,450<br>*-$33,528* | -$4,672<br>*-$45,404* | -$5,931<br>*-$57,641* |
| **Estimated change in services** | -17 | -35 | -53 | -71 | -91 |
| **Total costs to MBS** | -$1,114<br>*-$10,822* | -$2,264<br>*-$21,999* | -$3,450<br>*-$33,528* | -$4,672<br>*-$45,404* | -$5,931<br>*-$57,641* |
| **Total hospital costs** | -$74,457<br>*$26,401* | -$151,353<br>*$53,666* | -$230,674<br>*$81,792* | -$312,375<br>*$110,761* | -$396,569<br>*$140,614* |
| **Total costs to PHI** | **$redacted**<br>***$redacted*** | **$redacted**<br>***$redacted*** | **$redacted**<br>***$redacted*** | **$redacted**<br>***$redacted*** | **$redacted**<br>***$redacted*** |
| **Total overall cost** | **$redacted**<br>***$redacted*** | **$redacted**<br>***$redacted*** | **$redacted**<br>***$redacted*** | **$redacted**<br>***$redacted*** | **$redacted**<br>***$redacted*** |

*MBS=Medicare Benefits Schedule; Negative costs = savings. Negative services = reduced utilization; PHI=private health insurance*
Values in *italics* are the recalculated values based on the changes shown in Table 10
The ADAR applied the cost of revision surgeries to 'Total hospital costs' using a public AR-DRG-I16Z. The recalculated values apply a private payer AR-DRG- I16Z (as a cost to PHI) and MBS items 17610, 23045 and 48960 as costs to MBS.
Number of services of REGENETEN reflect the expected uptake of REGENETEN and the 'Estimated change in services' reflects changes in revision surgeries, based on the revision surgery rate specified in Table 78 pp155-156 in the ADAR
Source: *Compiled post ESC by Department from Commentary Recalculated spreadsheet*

*Evaluator's respecified financial model*

The financial implications of the Commentary's re-specified base case economic model is summarised in Table 16. The Commentary stated that the re-specified base case costs are 11% higher than the ADARs base case costs shown in italics in Table 13. As per ESC advice, the financial estimates were also presented for each subpopulation in Table 16.

**Table 16 Total costs to the MBS associated with REGENETEN - Re-specified base case- all populations (prevalence: 71/29% PTRCT/FTRCT)**

| - | 2020 | 2021 | 2022 | 2023 | 2024 |
|---|---|---|---|---|---|
| **REGENETEN** | - | - | - | - | - |
| Number of services- total | **redacted** | **redacted** | **redacted** | **redacted** | **redacted** |
| *PTRCT* | ***redacted*** | ***redacted*** | ***redacted*** | ***redacted*** | ***redacted*** |
| *FTRCT* | ***redacted*** | ***redacted*** | ***redacted*** | ***redacted*** | ***redacted*** |
| Sub-total direct cost to MBS | $0 | $0 | $0 | $0 | $0 |
| **Revision surgeries and anaesthesia costs for initial surgery** | | | | | |
| Estimated change in services | -29 | -59 | -90 | -122 | -155 |
| *PTRCT* | *-17* | *-35* | *-53* | *-71* | *-91* |
| *FTRCT* | -12 | -24 | -37 | -50 | -64 |
| Sub-total cost to MBS | -$13,849 | -$28,151 | -$42,904 | -$58,100 | -$73,759 |
| **Estimated change in services** | -29 | -59 | -90 | -122 | -155 |
| ***Total costs to MBS*** | ***-$13,849*** | ***-$28,151*** | ***-$42,904*** | ***-$58,100*** | ***-$73,759*** |
| *PTRCT* | *-$20,205* | *-$41,072* | *-$62,598* | *-$84,768* | *-$107,616* |
| *FTRCT* | *$6,357* | *$12,922* | *$19,694* | *$26,669* | *$33,857* |
| **Total hospital costs** | **-$39,601** | **-$80,500** | **-$122,688** | **-$166,141** | **-$210,921** |
| *PTRCT* | *-$66,002* | *-$134,166* | *-$204,480* | *-$276,902* | *-$351,536* |
| *FTRCT* | *$26,401* | *$53,666* | *$81,792* | *$110,761* | *$140,614* |
| ***Total costs to PHI*** | ***$redacted*** | ***$redacted*** | ***$redacted*** | ***$redacted*** | ***$redacted*** |
| *PTRCT* | *$redacted* | *$redacted* | *$redacted* | *$redacted* | *$redacted* |
| *FTRCT* | *$redacted* | *$redacted* | *$redacted* | *$redacted* | *$redacted* |
| ***Total overall cost*** | ***$redacted*** | ***$redacted*** | ***$redacted*** | ***$redacted*** | ***$redacted*** |
| *PTRCT* | *$redacted* | *$redacted* | *$redacted* | *$redacted* | *$redacted* |
| *FTRCT* | *$redacted* | *$redacted* | *$redacted* | *$redacted* | *$redacted* |

*Medicare Benefits Schedule; Negative costs = savings. Negative services = reduced utilisation*
*The ADAR applied the cost of revision surgeries to 'Total hospital costs' using a public AR-DRG-I16Z. The recalculated values apply a private payer AR-DRG- I16Z (as a cost to PHI) and MBS items 17610, 23045 and 48960 as costs to MBS.*
*Number of services of REGENETEN reflect the expected uptake of REGENETEN and the 'Estimated change in services' reflects changes in revision surgeries, based on the revision surgery rate specified in Table 78 pp155-156 in the ADAR.*
*The re-specified base case replaces the use of re-tear rate as a proxy for revision surgery with the revision surgery rate.*
*Source: and Compiled from Table 16, pxxvi of the Commentary, and post ESC by the Department using the Commentary Respecified spreadsheet*
*Italicised represents corrected values Post-ESC by Department*

In the pre-ESC response, the applicant acknowledges the changes made to the financial implications during the evaluation with three exceptions:

1. Re-tear rates are considered by the sponsor to be an appropriate proxy for revision surgeries in the economic and financial analyses, since reporting of revision rates in the clinical studies were subject to publication and population bias
2. The sensitivity analysis conducted by the evaluators assuming 100% of surgeries to be for full-thickness tears is misleading. As noted above, the expected proportion of all tears that are full-thickness tears is 60%. An assumption of 100% is therefore unrealistic
3. All evidence supports the use of one REGENETEN implant per tendon.

Nevertheless, the sponsor notes that the financial impacts for the re-specified base case – and in particular the impacts to PHI – do not differ substantially from those estimated by the sponsor in the ADAR.

*Noted Post ESC values*

As per ESC advice, the Department investigated the impact of prevalence on the financial estimates by performing additional sensitivity analysis using the prevalence estimate from Yeo 2019 (39% PTRCT, 61% FTRCT) provided initially in the pre-ESC response (Table 17).

**Table 17 Sensitivity analysis of financial estimates using prevalence 39/61% PTRCT/FTRCT from pre-ESC response**

| - | 2020 | 2021 | 2022 | 2023 | 2024 |
|---|---|---|---|---|---|
| **ADAR values** | | | | | |
| Total cost to MBS | *-$8,613* | *-$17,508* | *-$26,683* | *-$36,134* | *-$45,873* |
| Total hospital costs | *-$273,400* | *-$555,754* | *-$847,013* | *-$1,147,008* | *-$1,456,160* |
| Total PHI costs | *$redacted* | *$redacted* | *$redacted* | *$redacted* | *$redacted* |
| **Total overall costs** | ***$redacted*** | ***$redacted*** | ***$redacted*** | ***$redacted*** | ***$redacted*** |
| ***Commentary values -recalculated*** | | | | | |
| Total cost to MBS | *-$36,888* | *-$74,983* | *-$114,280* | *-$154,756* | *-$196,467* |
| Total hospital costs | *$20,329* | *$41,323* | *$62,980* | *$85,286* | *$108,273* |
| Total PHI costs | *$redacted* | *$redacted* | *$redacted* | *$redacted* | *$redacted* |
| **Total overall costs** | ***$redacted*** | ***$redacted*** | ***$redacted*** | ***$redacted*** | ***$redacted*** |
| ***Commentary values -respecified*** | | | | | |
| Total cost to MBS | *$2,540* | *$5,162* | *$7,868* | *$10,655* | *$13,526* |
| Total hospital costs | *$20,329* | *$41,323* | *$62,980* | *$85,286* | *$108,273* |
| Total PHI costs | *$redacted* | *$redacted* | *$redacted* | *$redacted* | *$redacted* |
| **Total overall costs** | ***$redacted*** | ***$redacted*** | ***$redacted*** | ***$redacted*** | ***$redacted*** |

*Source: Compiled post ESC by Department from Commentary Respecified spreadsheet*
*Italicised represents corrected values Post-ESC by Department*

## 14. Key issues from ESC for MSAC

| ESC key issue | ESC advice to MSAC |
|---|---|
| Primary outcome in the ADAR was imaging outcomes | The most appropriate primary outcome is function (and pain) improvement. There was no statistically significant differences in these patient-relevant outcomes. The clinical claim of superior effectiveness was only supported for imaging outcomes. |
| Very low-quality evidence for REGENETEN | Only 5 case series studies, limited to 2 Australian studies with n<30 and two international studies n>30 (PTRCT n =136; FTRCT n=115). The low quality evidence base is prone to multiple sources of bias; thus, there is low confidence in the estimate of effect. |
| *Naïve* indirect comparison | No randomised controlled trial, nor head-to-head data, the ADAR relied on *naïve* indirect comparisons. In addition, the meta-analyses had high heterogeneity, making interpretation challenging. This had flow on effects to the economic model and financial estimates. |
| 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). |
| Uncertainties that significantly impact the economic model | Highly uncertain and low-quality evidence base used to inform the model inputs. Other uncertainties included:<br>• Structural issues/assumptions related to use of imaging outcomes, physiotherapy visits and utilities favour REGENETEN. The modelled QALY benefit in both subpopulations was not validated in the ADARs evidence for clinical outcomes.<br>• Although the ADAR provided a more applicable estimate for prevalence of PTRCT/FTRCT (39/61%, respectively) in the pre-ESC response, this estimate was markedly different to the original estimate (71/29%, respectively); more evidence is required for this estimate, which impacts the derivation of the economics (and financials).<br>• The applicant's inclusion of the societal perspective (which was based on expert opinion), did not add much to decision making for MSAC. |
| Financial analysis | Uncertain, due to the flow of effects from clinical evidence and economic analyses, noting the Commentary's respecified base case was 20% higher than ADARs. ESC considered disaggregating the financial analysis for both subpopulations would be informative, given the differences in clinical and economic outcomes. |
| Upcoming cohort study in PTRCT high-grade (>50%) *vs*. standard surgery | Prospective, REGENETEN study (REGEN PUB 2018; NCT03734536) is due for completion in 2022, but applicant informed enrolment has been delayed. The primary outcome is the functional outcome: American Shoulder Elbow Surgeons (ASES) score at 3 months, and 24 months. Although this is a comparative study, it is a non-randomised, unblinded and industry funded study that might not substantially change our confidence in the estimate of effect. |

### ESC discussion

ESC noted that this application was referred to MSAC by the Prosthesis List Advisory Committee (PLAC), as REGENETEN is a novel, costly device that requires a full health technology assessment.

ESC noted the lack of consumer response and therefore there is no patient experience information for MSAC to consider.

ESC noted that this is an application for listing on the Prostheses List (PL), not a new Medicare Benefits Schedule (MBS) item. There are MBS item numbers in use (48960, 48906, 48909) that could be used if this device was found to be safe and cost-effective. ESC noted the applicant developed assessment report's (ADARs) claim that this is to be a once-only procedure; however, this cannot currently be restricted by the proposed MBS item numbers. ESC queried if this could be restricted by private insurers stipulating limits on use on PL (e.g. once per lifetime). Although, ESC noted the pre-ESC response, which the

applicant indicated that the real-world clinical evidence for REGENETEN suggests that only one implant is used during surgery.

ESC noted there were no randomised controlled trials (RCTs), nor head-to head evidence evaluating REGENETEN *vs.* standard surgery in both subpopulations. Hence, all comparisons were *naïve* indirect comparisons, that were not adjusted via any common comparator. ESC noted: the evidence for REGENETEN is derived from only case series studies (k=5; n=251), further divided into the subpopulations, which the majority had small sample sizes (n<30), including the two Australian studies; and the evidence for standard surgery was from RCTs and observational studies (k=45; n=3,209). Overall, ESC considered that the *naïve* indirect comparison was at very high risk of bias, noting the ADAR did not fully address these issues. In addition, many of the ADARs meta-analyses had high heterogeneity, making interpretation challenging.

Regarding comparative safety, ESC noted the scarcity of long-term safety data from clinical studies, which was limited to 11 patients followed over 5 years in subpopulation 1 (PTRCT) and only follow-up data for 2 years in subpopulation 2 (FTRCT). ESC also noted that the claim of non-inferiority in comparative safety for subpopulation 2 was not supported by the statistically significantly higher revision surgery rates with REGENETEN, which in the pre-ESC response, the applicant indicated this was driven by the medico-legal environment of the US study (McIntyre 2019). The applicant also highlighted concerns of publication bias among standard surgery studies, which would bias against REGENETEN.

Regarding comparative effectiveness, ESC considered that the appropriate primary outcomes are clinical outcomes assessing function, quality of life, pain and range of movement scores (e.g. American Shoulder Elbow Surgeons score; ASES score], rather than imaging outcomes, which ESC noted the included studies had heterogeneous definitions for these outcomes. ESC also noted the claim of superiority in clinical effectiveness was based on statistically significant greater benefit in imaging outcomes, rather than in clinical or functional outcomes (as per clinical claim), the results of which were not statistically significant. ESC considered the pre-ESC response, which the applicant reasoned the results for functional outcomes could be due to the heterogeneity in baseline characteristics included in the *naïve* comparisons, and due to the studies were not powered to detect differences in clinical or patient-relevant outcomes. However, ESC noted no power calculations were undertaken for REGENETEN studies, as they were case series data. Overall, ESC considered that more evidence of clinical outcomes in both subpopulations is required.

ESC considered that the key uncertainty with the economics related to the very low quality evidence informing the key model inputs, noting the ADARs model relied heavily on imaging outcomes. ESC noted the following structural issues with the model:

- No conceptualisation process or strong justification for the health states in the model was provided; choosing health states on the basis of available data is inappropriate
- Revision surgery rates should be included in the model, and that the re-tear rate should be separated from re-surgery rate
- Whether the use of two different models for each subpopulation in the economic evaluation was appropriate, noting patients can progress from a partial thickness tear to a full thickness tear, which this approach does not consider.

ESC agreed with the Commentary who considered the model structure used is not well justified due to a number of issues with the chosen health states and the ability to accurately reflect utility values for these health states. The relationship between revision surgery, incomplete healing and re-tear rates is not well defined or supported by the evidence. ESC

also agreed with the Commentary that the source of utility values is highly uncertain and also noted that modelled rehabilitation outcomes (e.g. physiotherapy sessions) were based on expert opinion. ESC noted that the Commentary's respecified base case model attempted to address some of these issues resulting in much higher incremental cost-effectiveness ratio's (ICERs) for both subpopulations (see Table 9); however, ESC considered the ICERs still remained highly uncertain, mainly due to the lack of good quality evidence informing the model.

ESC considered another source of uncertainty affecting the derivation of the economics (and the financials) was the ADARs estimate of prevalence of PTRCT/FTRCT in the proposed population. ESC noted in the pre-ESC response, the applicant provided a more applicable estimate from an Australian retrospective cohort study (39/61%, respectively), which increased confidence in the prevalence estimates (and improved the ICER for REGENETEN), but ESC was concerned how this estimate was markedly different to the original estimate provided in the ADAR (71/29%, respectively). ESC considered that more evidence was required for this estimate, given the difference in ICERs of both subpopulations from the healthcare perspective system (ADAR and Commentary respecified base case ICER: PTRCT > FTRCT), and its consequential impact to the pooled ICER, relevant to the proposed population for public funding.

ESC also noted the ADARs economic analyses did not define a base case perspective but rather included an assessment from the healthcare system and societal perspective. ESC considered that given the absence of good quality evidence, and no comparative evidence for assessing outcomes captured in the societal perspective (the ADAR relied on expert opinion), including the societal perspective did not add much value to decision making for MSAC. Consequently, ESC advised the healthcare system perspective should inform the base case.

Consistent with the economics, ESC noted that the Commentary respecified the financial base-case analysis. ESC noted the budget impact may be approximately 20% higher compared to the estimate from the ADAR. Moreover, ESC considered that due to the uncertainty with the clinical evidence, which had flow on effects to the economic model, that the financial estimates were also uncertain. However, ESC noted the financial impact was modest (including to the MBS). ESC also noted that the financial estimates were not updated for the applicant's updated prevalence estimate provided in the pre-ESC response. ESC also considered that the financial analyses should be disaggregated for subpopulation 1 and subpopulation 2, given the differences in ICERs, uncertainty with estimate of prevalence, and also differences in cost offsets, as REGENETEN is performed as an alternative to standard surgery in subpopulation 1, compared with as an additional procedure in subpopulation 2. Post ESC, all financial estimates were disaggregated for each population using the ADARs original estimate of prevalence (71/29% PTRCT/FTRCT, respectively) [see Tables 13-15]; and sensitivity analysis was conducted using the prevalence estimate provided by applicant in the pre-ESC response (39/61% PTRCT/FTRCT, respectively) [see Table 16].

ESC noted possible new evidence on the horizon (REGEN PUB 2018; NCT03734536:), which the primary outcome in this study will be the ASES score at 3 months and 24 months. However, enrolment is delayed (until possibly 2022), and ESC considered that the nonrandomised, unblinded, industry-funded study may not substantially change the confidence in the estimate of the effect.

## 15. Other significant factors

As noted by the PASC in August 2019, the Commentary stated that there is an upcoming nonrandomised prospective study comparing REGENETEN and standard arthroscopic repair of patients with high-grade (>50%) PTRCT (subpopulation 1) due for completion in September 2020 (REGEN PUB 2018, NCT03734536). The primary outcome is the American Shoulder Elbow Surgeons (ASES) score at 3 months following index surgery, with secondary outcomes including (but not limited to) ASES score up to 24 months, Single Assessment Numeric Evaluation (SANE) score up to 24 months, cumulative pain medication, incidence of revision surgery and aggregate healthcare utilisation costs.

In the pre-ESC response, the applicant advised that this trial is delayed due to enrolment issues. First year results are expected **redacted**.

## 16. Applicant comments on MSAC's Public Summary Document

Smith & Nephew is disappointed with the outcome from this MSAC evaluation of REGENETEN for Prostheses Listing given the need for a new treatment option in patients with symptomatic partial-thickness (PTRCT) or full-thickness rotator cuff tear (FTRCT) who have failed at least three months of conservative, non-surgical management and are considered eligible for surgical repair. Smith & Nephew is committed to working with the Department of Health to achieve Prostheses Listing at the earliest opportunity to ensure that appropriate Australian patients with PTRCT or FTRCT can have timely and equitable access to REGENETEN in line with its TGA registration (effective July 2020).

## 17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: visit the MSAC website