

MSAC Application 1593.1

Bioinductive implant for the repair of rotator cuff tear

PICO Confirmation

Summary of PICO criteria to define questions to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

Table 1 PICO for bovine bioinductive collagen implant in patients with symptomatic partial-thickness rotator cuff tear: PICO set 1

Component	Description
Population	<p>Patients with symptomatic partial-thickness rotator cuff tear (PTRCT) who:</p> <ul style="list-style-type: none"> • have failed at least 3 months of conservative management (not responded to pain relief^a, modified daily activities and physical therapy); and • are considered eligible for (or indicated for) surgical repair <p>An understanding of the natural history of rotator cuff pathology should inform the eligible population.</p>
Intervention	<p>Arthroscopic surgery with use of bovine bioinductive collagen implant (BCI). (Standard repair with sutures or anchors is typically not required with use of bovine BCI in this population (e.g. debridement + bursectomy + bovine BCI).)</p>
Comparator	<p>Standard arthroscopic surgical repair (without bovine BCI), with repair performed using standard sutures or anchors, using two techniques:</p> <ul style="list-style-type: none"> • Take-down repair; OR • Trans-tendon repair <p>AND</p> <p>Continued conservative management without surgical repair</p>
Outcomes	<p>Safety</p> <ul style="list-style-type: none"> • Adverse events • Procedural complications • Longer-term adverse events • Revision surgery <p>Clinical effectiveness</p> <p><i>Functional outcomes</i></p> <ul style="list-style-type: none"> • American Shoulder and Elbow Surgeons standardized Form for the Assessment of the Shoulder (ASES) • Constant-Murley shoulder score • Oxford Shoulder Score (OSS) • Visual Analogue Scale (VAS) pain • Post-operative physical therapy • Post-operative return to activities • Single Assessment Numeric Evaluation (SANE) • Progression to full-thickness tear • Western Ontario Rotator Cuff (WORC) index • Quality of Life <ul style="list-style-type: none"> ○ EuroQol-five dimension scale (EQ-5D) ○ Short Form-36 Health Survey (SF-36) <p><i>Secondary effectiveness outcomes</i></p> <ul style="list-style-type: none"> • Length of hospital stay • Time to return to work • Opioid Consumption

Component	Description
	<p><i>Imaging-based outcomes</i></p> <ul style="list-style-type: none"> • Tendon thickness • Size of the cuff defect (tear size, re-tear rate) <p>Cost-effectiveness</p> <ul style="list-style-type: none"> • Cost per life-year gained • Cost per quality-adjusted life-year (QALY) gained <p>Healthcare resources</p> <ul style="list-style-type: none"> • Cost of intervention delivery • Cost associated with changes in clinical management (e.g., follow-up) <p>Total Australian Government healthcare costs and out of pocket costs</p> <ul style="list-style-type: none"> • Total cost to the Medicare Benefits Schedule (MBS) • Total cost to other healthcare services • Total projected annual Prescribed List of Medical Devices and Human Tissue Products (PL) benefits claimed • Out of pocket costs
Assessment questions	What is the safety, effectiveness and cost-effectiveness of arthroscopic surgery with use of bovine bioinductive collagen implant versus (i) standard arthroscopic surgical repair, and (ii) continued conservative management, in patients with symptomatic partial-thickness rotator cuff tear?

BCI = bovine bioinductive collagen implant; PTRCT = partial-thickness rotator cuff tear

^a Including nonsteroidal anti-inflammatory drugs (NSAIDs) ± corticosteroid injections

Table 2 PICO for bovine bioinductive collagen implant in patients with symptomatic full-thickness rotator cuff tear: PICO set 2

Component	Description
Population	<p>Patients with symptomatic full-thickness rotator cuff tear (FTRCT) who:</p> <ul style="list-style-type: none"> • have failed at least 3 months of conservative management (not responded to pain relief^a, modified daily activities and physical therapy); and • are considered eligible for (or indicated for) surgical repair <p>An understanding of the natural history of rotator cuff pathology should inform the eligible population.</p>
Intervention	Arthroscopic or 'mini-open', standard surgical repair with use of bovine BCI ^b . (Standard repair with sutures or anchors is required with use of bovine BCI in this population (e.g. debridement + bursectomy + surgical repair + bovine BCI).)
Comparator/s	Standard surgical repair (without bovine BCI), with repair performed using standard sutures or anchors, performed arthroscopically or with 'mini-open' approach
Outcomes	<p>Safety</p> <ul style="list-style-type: none"> • Adverse events • Procedural complications • Longer-term adverse events • Revision surgery <p>Clinical effectiveness</p> <p><i>Functional outcomes</i></p>

Component	Description
	<ul style="list-style-type: none"> • American Shoulder and Elbow Surgeons standardized Form for the Assessment of the Shoulder (ASES) • Constant-Murley shoulder score • Oxford Shoulder Score (OSS) • VAS pain • Post-operative physical therapy • Post-operative return to activities • Single Assessment Numeric Evaluation (SANE) • Progression to full-thickness tear • Western Ontario Rotator Cuff (WORC) index • Quality of Life <ul style="list-style-type: none"> ○ EuroQol-five dimension scale (EQ-5D) ○ Short Form-36 Health Survey (SF-36) <p><i>Secondary effectiveness outcomes</i></p> <ul style="list-style-type: none"> • Length of hospital stay • Time to return to work • Opioid Consumption <p><i>Imaging-based outcomes</i></p> <ul style="list-style-type: none"> • Tendon thickness • Size of the cuff defect (tear size, re-tear rate) <p>Cost-effectiveness</p> <ul style="list-style-type: none"> • Cost per life-year gained • Cost per quality-adjusted life-year (QALY) gained <p>Healthcare resources</p> <ul style="list-style-type: none"> • Cost of intervention delivery • Cost associated with changes in clinical management (e.g., follow-up) <p>Total Australian Government healthcare costs and out of pocket costs</p> <ul style="list-style-type: none"> • Total cost to the Medicare Benefits Schedule (MBS) • Total cost to other healthcare services • Total projected annual Prescribed List of Medical Devices and Human Tissue Products (PL) benefits claimed • Out of pocket costs
Assessment questions	What is the safety, effectiveness and cost-effectiveness of arthroscopic surgery with use of bovine bioinductive collagen implant versus standard arthroscopic surgical repair in patients with symptomatic full-thickness rotator cuff tear?

BCI = bovine bioinductive collagen implant; FTRCT = full-thickness rotator cuff tear

^a Including nonsteroidal anti-inflammatory drugs ± corticosteroid injections

^b The primary reason for use of REGENETEN is to repair rotator cuff tears in appropriate patients. The proposed TGA indication is REGENETEN Bioinductive Implant for the management and protection of rotator cuff tendon injuries in which there has been no substantial loss of tendon tissue. The applicant agreed to incorporate wording from the proposed TGA indication into the eligible population description (i.e. rotator cuff tears where there has been no substantial loss of tendon tissue).

Purpose of application

An application requesting listing on the Prescribed List of Medical Devices and Human Tissue Products (PL) (formerly the Prostheses List) of REGENETEN bioinductive collagen implant (BCI) for the repair of rotator cuff tear was received from SMITH & NEPHEW PTY LIMITED by the Department of Health. This is a re-submission of a previous application (MSAC 1593) from 2020.

There are currently several clinically appropriate MBS items that allow Medical Devices and Human Tissue Advisory Committee (which has replaced the Prostheses List Advisory Committee, PLAC)-approved product/device use. If this technology is deemed safe, effective and cost effective for use in the nominated indications, those existing MBS items would be used.

The applicant expects that compared to standard arthroscopic surgical repair, arthroscopic surgery with use of bovine bioinductive collagen implant for the treatment of patients with symptomatic rotator cuff tear will have:

- Superior clinical effectiveness in selected patients
- Non-inferior safety.

The rationale for this claim are the results from the REGENETEN clinical trial program which demonstrated that patients in the REGENETEN arm experienced significantly lower re-tear rates, significantly lower failure rate at the musculotendinous junction, lower post-operative fatty infiltration, no difference in complications between groups, improvement in function and pain scores (Constant-Murley Shoulder Score and VAS pain score assessments) compared to the control group (standard surgical repair).(Ferreira Barros, 2022; Iban, 2022).

Background

In July 2020, MSAC did not support public funding for bovine bioinductive collagen implant (REGENETEN; application 1593) for the repair of rotator cuff tear. MSAC advised the then 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.

MSAC considered that the applicant would need to provide high quality evidence before they could resubmit to MSAC¹.

For the resubmission, the applicant requested an expedited pathway assessment for both populations on the basis that the proposed PICO is very closely aligned to the previously ratified PICO (September 2019). After meeting with the applicant on 3 March 2023, the department sought MSAC Executive advice for the progression of the planned resubmission, including pathway advice at its 21 April meeting.

At its April 21 meeting, the MSAC Executive advised that PASC consideration is required to confirm the PICO for the resubmission however, only a focused approach is required regarding the definition of the patient population and the comparator. This includes:

1

[http://www.msac.gov.au/internet/msac/publishing.nsf/Content/0C84CF025ADD24DBCA258426001C4D41/\\$File/1593%20-%20Ratified%20PSD_Jul2020_redacted.docx](http://www.msac.gov.au/internet/msac/publishing.nsf/Content/0C84CF025ADD24DBCA258426001C4D41/$File/1593%20-%20Ratified%20PSD_Jul2020_redacted.docx)

- defining the duration of failure to conservative management in the eligible population, and
- considering whether continued conservative management may be an additional comparator due to the intervention being used without standard surgical repair in subpopulation 1 (PTRCT).

Both of the points raised by the MSAC Executive are discussed in the relevant sections of the Draft PICO.

PICO criteria

Population

The intervention is intended for patients with a rotator cuff tear, the partial or full detachment of the tendon that attaches the muscles from the shoulder blade to the head of the humerus. Eligible patients would not have responded to conservative (i.e. non-surgical) management, including pain relief (e.g. nonsteroidal anti-inflammatory medication (NSAIDs) ± corticosteroid injections), modified daily activities and physical therapy.(1, 2)

The two populations (PICO sets) relevant for this application are defined by the depth of the rotator cuff tear:

- **Population 1:** Patients with symptomatic **partial-thickness** rotator cuff tear (PTRCT) who have failed at least three months of conservative (non-surgical) management; and
- **Population 2:** Patients with symptomatic **full-thickness** rotator cuff tear (FTRCT) who have failed at least three months of conservative (non-surgical) management.

The distinction of the two populations is important, given current approaches to surgical management differ, based on if the tear is partial or full-thickness. (1, 2)

*PASC noted that the two populations are patients with **symptomatic** partial-thickness or total-thickness rotator cuff tear, requiring failed conservative management for **at least three months** to become eligible for surgery.*

PASC noted that according to clinician advice, in practice the time from first onset of symptoms to presentation to an orthopaedic surgeon is highly variable, with many patients presenting after more than six months of pain. However, the three-month period is accepted in research and commonly reported in the literature.

Given the variable nature of rotator cuff tears, PASC agreed that the time frame of a minimum of three months of conservative management is reasonable.

Defining rotator cuff tears

The rotator cuff provides glenohumeral joint stability.(3) It comprises a group of four muscles and their tendons (supraspinatus, infraspinatus, teres minor, and subscapularis) at the shoulder joint, forming a multilayered horseshoe shape cuff around the head of the humerus bone.(4)

Rotator cuff injury can range from simple inflammation to tears of the muscles or tendons. Rotator cuff tears may result due to a degeneration of the tendon quality or due to trauma, where a tear arises from a major injury to otherwise healthy tissue. Most common are degenerative tears due to the progression of chronic tendinosis, which may or may not be symptomatic.(3) However, rotator cuff tears usually occur as a result of trauma, and are rare in the young (age<35 years).(5)

Several risk factors have been identified in predisposing individuals to the development of rotator cuff tears; increasing patient age, smoking, hypercholesterolemia, and family history. The Applicant stated that each of these may play an additive role to the underlying influence of age-related degeneration in the development of rotator cuff disease.

The Applicant indicated that REGENETEN™ is not intended to be used in acute trauma.

Population 1: partial-thickness rotator cuff tear

PTRCTs do not extend through the full-thickness of the tendon. They can involve any of the four rotator cuff tendons and are typically classified by location: articular sided, bursal side, or intratendinous (which are only seen on imaging) (6). Subclassification includes the size (or depth) of the tear, which can be represented as percentage of the tendon thickness torn. The Ellman classification system (7) classifies PTRCTs by determining the amount of exposed articular footprint. Specifically, Grade I (*low*): < 3mm (<25% tendon thickness); Grade II (*medium*): 3-6mm (25-50% tendon thickness); and Grade III (*high*): >6mm (>50% tendon thickness, but not full-thickness); **Error! Reference source not found.** in Appendix) (6, 8). While widely accepted, this classification system does not take into account a number of factors including: an analysis of tissue quality, the area of tearing (i.e., not just thickness but anterior to posterior and medial to lateral), or the aetiology of the tear itself (8). In addition, controversy exists around the amount of footprint needed for a tear to be classified as a 50% partial-thickness tear (6).

The Applicant stated that the literature demonstrates that articular-sided tears, which can be subclassified as partial articular-sided rotator cuff tears (PASTA), are at least twice as common as bursal-sided tears, and that most tears involve the supraspinatus tendon.(9)

Partial-thickness tears are 2-3 times more likely, and often much more painful, than full-thickness tears (10), where the tendon is no longer connected to the bone.

Spontaneous healing of untreated rotator cuff tears is rare (11-13), and without intervention, a partial-thickness tear is likely to enlarge and propagate into full-thickness tears (14, 15). Progression of symptomatic partial-thickness tears to full-thickness tears 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.(16) Because increased tear size and poorer muscle quality are associated with poorer healing after surgical repair, repair before progression may improve outcomes.(13) The risk of tear progression has been shown to correlate with percentage tendon thickness at presentation with progression observed in 55% of patients with ≥ 50% tearing of tendon thickness at presentation compared to 14% tear progression in those who had < 50% tearing.(17)

Population 2: full-thickness rotator cuff tear

FTRCTs involve the full detachment of the tendon that attaches the muscles from the shoulder blade to the head of the humerus. They can be classified by the DeOrio and Cofield classification system (18), which classifies FTRCT are either small (< 1cm), medium (1-3cm), large (3-5cm) and massive (>5cm)². However, some prefer to classify a massive tear as involving two or more tendons; usually the supraspinatus and infraspinatus, but also supraspinatus and subscapularis.(5)

Current management of rotator cuff tears

Typically, patients with rotator cuff tears present to their general practitioner with shoulder instability, pain and/or weakness and decreasing shoulder power and function.(15) Rotator cuff tears most frequently occur with general wear and tear, and most people cannot remember injuring their shoulder. These

² Measured by the length of the greatest diameter of the tear

“degenerative tears”, if not associated with arm weakness, may be successfully treated without surgery. Medical treatment is always the first management option of degenerative tears of rotator cuff tendons (3), and can involve avoiding overhead activities, regular simple pain relief (e.g. NSAIDs) and gentle physiotherapy. In more severe cases, increased pain relief using corticosteroid injections, may be used (19). If a rotator cuff tear is suspected, early referral to a physiotherapist may be appropriate.(20) Referral for imaging (i.e. X-ray AND/OR ultrasound AND/OR MRI) may also be warranted where there is evidence or suspected serious damage/disease.(5, 21). The Applicant stated that MRI is typically used in most cases to diagnose PTRCTs and FTRCTs. All patients in Bokor et al (1, 2) had preoperative MRI scans.

The decision to perform surgical repair is dependent on clinical and morphological factors, and patient characteristics, patient eligibility and preference.(3) Specifically, the orthopaedic surgeon will determine treatment strategies for the rotator cuff repair primarily based on the location, anatomy and the size of the defect, with ‘surgery timing’, functionality, age and gender as important secondary considerations.(19)

Failure of anatomic repairs is reportedly 20-40% after primary rotator cuff repairs and is even higher in revision cases. Re-tear of a rotator cuff repair has been associated with a multitude of factors including patient age, tear dimensions, and tendon tissue quality.(22) A recent study found that re-tears following rotator cuff repair primarily occurred between 6-26 weeks, with a substantial number of re-tears occurring between 12-26 weeks.(23) With over one-quarter of repairs failing to achieve durable integrity (i.e. re-tears) of the rotator cuff at two years (24), the inability to obtain high healing rates has spurred the investigation of biological options to augment rotator cuff repairs (25), e.g. application of bovine bioinductive implants in surgical repair of rotator cuff tears.

However, some patients may not be eligible for surgery or may have a preference to not have surgery. In this instance, conservative management is continued.

Duration of failure to conservative management

Conservative management should include a combination of strategies to reduce inflammation, alleviate pain, and correct underlying dysfunction, including physical therapy and at least one complementary conservative treatment strategy (26). Surgical repair is considered when symptoms fail to improve after a certain period of conservative treatment. The applicant proposed a minimum of 3 months of conservative treatment based on currently available guidelines.

In the AIM 2021 guideline (26) the failure of conservative treatment requires ALL of the following:

- Patient has completed a full course of conservative management for the current episode of care
- Worsening of or no significant improvement in signs and/or symptoms upon clinical re-evaluation
- More invasive forms of therapy are being considered.

Recent clinical guidelines review on management of rotator cuff disease, carried out as part of the MSAC Application 1711³, identified two guidelines (AIM 2021, Washington State Department of Labor and Industries 2018) for chronic full-thickness-tear. Both indicated that surgery may be considered with similar criteria to acute full-thickness-tear (a review of pain, weakness, physical examination and imaging, with or without X-ray) but with the addition of failure of at least 6 weeks conservative therapy.

The clinical guidelines review further reported that for partial-thickness tear repair, patient selection for surgery is generally based on presentation including pain, weakness, exam, imaging, and failure of conservative therapy. Certain guidelines recommend that with partial-thickness tear of less than 50%

³ [1711 Clinical Guidelines Review.docx \(live.com\)](#)

thickness an additional 6 weeks conservative therapy is required prior to considering surgery (Hohmann et al. 2020, Washington State Department of Labor and Industries 2018). One guideline considers surgical repair to be an option where there has been no improvement in function after 6 to 12 weeks (Colorado Department of Labor and Employment 2015).

It should be noted that the proposed duration of treatment failure is based on current clinical practice but evidence on whether this may be the most appropriate time is not available in the current literature (27). In one small study evaluating physical therapy for symptomatic rotator cuff tear, a threshold of 16 physical therapy sessions was observed for pain and functional improvement during follow-up, after which significant improvement was not seen (28).

The MSAC Executive noted that duration of failure to conservative management of at least 3 months in this re-application was different to conservative management for a period of 6 months in application 1711.

PASC was requested to advise whether the duration of the condition and interval of failure to conservative management as a potential treatment effect modifier be investigated in the assessment by potentially including all relevant trials/clinical studies irrespective of the duration of symptoms.

Burden of disease

Rotator cuff tears are the most common cause of pain and disability related to the shoulder but can also be asymptomatic. The incidence of cuff tears ranges from 5 to 40% (29, 30); however, given that some rotator cuff tears are asymptomatic, the true incidence is difficult to determine. Approximately one third of silent rotator cuff tears will become symptomatic (31).

The prevalence of rotator cuff tear increases with age; rotator cuff tears are present in approximately 25% of individuals in their 60s and 50% of individuals in their 80s (13).

If left untreated, shoulder problems and pain can lead to significant disability, limitations in activity and restrict participation in major life areas such as work and employment, education, community, social and civic life.

PASC queried why given that the prevalence of rotator cuff injuries goes up with age (being highest for the 80+ age group), the average age of participants in the trials cited by the applicant was in the mid-50s with a maximum age of around 75 and whether the research cited was representative of the population that would be most affected by rotator cuff injuries. PASC further queried whether there should be age restrictions for the proposed population in light of these epidemiological trends.

However one of the clinical experts supporting the applicant clarified that the oldest age groups (80+) with rotator cuff injuries typically do not opt for rotator cuff repairs and therefore would not be considered the target population for REGENETEN. Instead it would be the younger age groups with this condition who would consider undertaking rotator cuff repairs as they have more active lifestyles. PASC considered this reasonable.

Utilisation estimates

As per ratified PICO 1593, a market share approach is inappropriate as item 48960 (which was considered by PASC as the most applicable item given it refers to arthroscopic repair) also includes shoulder reconstruction, resection, and replacement services, therefore, using this approach would likely overestimate the eligible population for BCI in rotator cuff surgical repair.

Therefore, an epidemiological approach estimating the expected utilisation of BCI in rotator cuff surgical repair in Australia over the next four years will be used to estimate utilisation. The applicant applied the

incidence of 131 of 100,000 rotator cuff repairs from a population-based study in Finland (32) to the current adult Australian population estimates from the Australian Bureau of Statistics (ABS) (3222.0 Series B (Australian Bureau of Statistics, 2018)).

The Applicant then derived the proportion of procedures that would be performed in the private setting using the estimate that 45.1% of the Australian population are privately insured in December 2022 (Australia Prudential Regulation Authority, 2022); a total of 12,550 rotator cuff repairs would be performed in Year 1 (2024). The Applicant has assumed a Redacted % uptake rate in Year 1, which would increase linearly to Redacted % in Year 4 (2027). Uptake rate estimates have been based on assumption, and not evidence, however, the application indicated this will be validated by primary research with Australian surgeons in the assessment phase.

The Applicant stated that there are no apparent constraints in the health care system that would impact on uptake.

As per 1593 Ratified PICO, the Applicant expects the risk of leakage to be low. It is acknowledged that ESC was previously concerned about leakage, prompting MSAC to suggest in the 1593 PSD “the relevant authorities may wish to consider introduction of measures to implement a once-only per shoulder restriction” (PSD, p5).

The Applicant has acknowledged ESC and MSAC’s leakage concern and acknowledges notes in the I.S.Mu.L.T (Italian Society of Muscles, Tendons and Ligaments Rotator Cuff Tear Guidelines) that, while diagnostic accuracy of MRI for detection of FTRCTs is excellent, it is more limited for PTRCTs (19). However, the applicant would like to state that this is not the current standard of care for patients who are not symptomatic or who have not yet undertaken conservative management to be referred to an orthopaedic surgeon. It is unlikely that patients without symptoms would elect to undergo surgery. In the event that symptoms fail to improve following a minimum of 3 months of conservative treatment, or where a tear has occurred from sudden trauma or acute injury and is impacting on comfort and function, referral to an orthopaedic surgeon for further review and possible surgical repair of the tear is then indicated.(20)

A REGENETEN registry (Amplitude) has been established to capture data to demonstrate the real-world value of the device. Data has been captured from the United Kingdom and Hong Kong, with Australian patients to be included as of April 2023. The intention of this registry is to further support and evaluate the health economic impact of REGENETEN and evaluate the patient reported outcome measures to demonstrate how REGENETEN is improving outcomes for patients. Furthermore, data from this registry will be used to support utilisation estimates and demonstrate the ‘once per shoulder’ frequency of REGENETEN and to demonstrate the low leakage risk. The Applicant is willing to work with the relevant authorities to aid in ensuring a ‘once-per shoulder’ restriction as was recommended by MSAC in the ratified PSD.

Intervention

The proposed intervention is the use of bovine bioinductive implants (REGENETEN™) in addition to:

- arthroscopic surgery (e.g. debridement and bursectomy, without standard surgical repair) in **Population 1**; and
- arthroscopic or ‘mini- open’ standard surgical repair (e.g. debridement and bursectomy, plus standard surgical repair with sutures or anchors) in **Population 2**.

Feedback from the Applicant (33), indicated that REGENETEN™ is not used as an adjunct to surgical repair of the rotator cuff. Its use is central in this procedure in both populations.

The Applicant stated that the bovine bioinductive collagen implant is designed to induce the formation of new tendon-like tissue that will biologically augment the degenerated rotator cuff tendon. The Applicant claimed the physical and chemical properties of the scaffold provide a layer of collagen between a flat tendon and the surrounding tissue, permitting collagen in-growth into the scaffold and promoting collagen re-modelling, with alignment of the collagen fibres in the direction of stress in the tendon (i.e. promote tendon vascularisation and growth).

PASC noted that the proposed intervention is the implantation of a bioinductive collagen implant, whereby in Population 1 the implant would replace the suture or anchor, and in Population 2 the implant would be used in addition to the standard repair.

Procedure

The procedure is performed under general anaesthetic (2) in the hospital inpatient setting (private and public), with overnight hospitalisation. The procedure can be performed arthroscopically (minimally invasive keyhole surgery) or as mini-open surgery (which involves a small incision typically 3 to 5 cm long). The Applicant stated that arthroscopic and mini-open repair surgical techniques are associated with similar outcomes, with both being able to be used interchangeably, depending on patient and rotator tear characteristics (34, 35). This is similar to recommendations in the *I.S.Mu.L.T 'Rotator Cuff Tear Guidelines'* which state there are no statistically significant differences between the two techniques, in terms of relapse, complications and functional outcomes (19).

PASC noted the advice from one of the clinical experts supporting the applicant that the intervention is not a less invasive option to standard surgical repair.

Based on expert opinion, the average duration of surgery (i.e. with use of REGENETEN) is 15-30 minutes, for either partial-thickness or full-thickness repairs [Application Form, p20]. However, for **Population 1**, this is performed in phase three of the surgical repair procedure (as standard surgical repair with sutures or anchors is not required in this population); and for **Population 2**, this is performed in phase four of the surgical repair procedure (as surgical repair with sutures or anchors is required in addition to bovine BCI). *If surgical repair is performed, this is immediately prior to applying bovine BCI (1, 25).* The Applicant's summary of the phases required for surgery in each population is provided in Table 3.

Table 3 Description of surgical procedures with use of bovine bioinductive collagen implants in both populations

-	Population 1	Procedure time	Population 2	Procedure time
Phase 1	Anaesthesia and skin penetration	-	Anaesthesia and skin penetration	-
Phase 2	Debridement, diagnosis and bursectomy	-	Debridement, diagnosis and bursectomy	-
Phase 3	Arthroscopic surgical repair with REGENETEN	15-30 minutes	Standard arthroscopic or mini-open surgical repair (Sutures or anchors) ^a	30-60 minutes ^a
Phase 4	N/A	N/A	Arthroscopic surgical repair with REGENETEN	15-30 minutes

Source: Applicant feedback

N/A = not applicable

^a As per comparator; refer to comparator section for description of these surgical procedures

The Applicant stated that, for both populations, the proposed intervention is intended to be performed once.

The procedure is performed by orthopaedic surgeons. The Applicant and its nominated clinical expert confirmed at PASC of the 1593 submission, that no additional training is required by orthopaedic surgeons to use REGENETEN in appropriate patients. However, this should be verified during the assessment phase.

The Applicant also provided the detailed surgical steps in arthroscopic use of REGENETEN™ (as published in Wasburn et al. 2017 (14) (see below) and provided this schematically in Figure 1:

1. Diagnostic arthroscopy is performed.
2. Tendon markers along the anterior edge of the supraspinatus are placed in a percutaneous fashion.
3. Entry is made into the subacromial space, and bursectomy is performed through a standard lateral portal.
4. A 5-mm guidewire is placed at the lateral edge of the rotator cuff footprint.
5. The graft is hydrated (in saline) for one minute
6. The graft is loaded into the delivery instrument.
7. The graft is introduced until the red button becomes prominent.
8. The graft is deployed.
9. A second lateral cannula is placed just off the lateral edge of the acromion.
10. Soft-tissue staples are placed through the graft into the underlying rotator cuff.
11. The tendon markers are removed.
12. A bone stapler awl is used to tension the graft from the lateral portal.
13. The bone staples are placed.
14. The instruments are removed, and the wounds are closed [Application Form, p12]

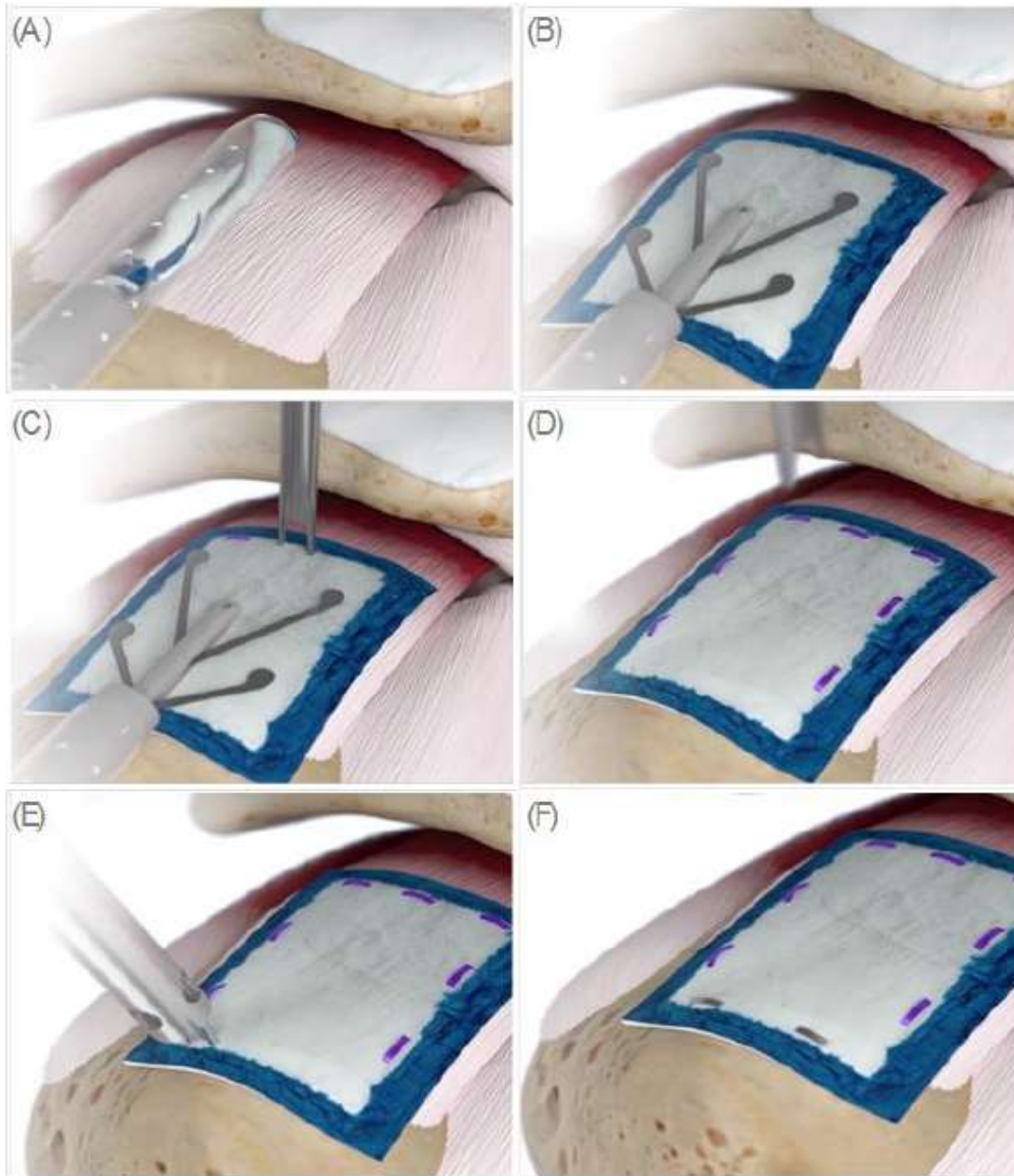


Figure 1 Application of bovine bioinductive collagen implant (using REGENTEN™)

Source: Applicant feedback (33)

Legend: A. Bioinductive Implant Placement Cannula insertion; B. Bioinductive Implant Placement deployment; C. Tendon Anchor insertion at medial edge; D. Completed Tendon Anchor insertion at posterior and anterior edges; E. Bone Anchor insertion at lateral edge; F. Fully fixated REGENTEN Bioinductive implant

Note, the equipment required includes standard arthroscopic equipment, the Bovine Bioinductive Implant System and an 8-mm cannula.(14) The Applicant stated that single use consumables included: three clear cannulas, and disposable instrument set comprising: two clear lateral cannulas, guide wire, graft delivery system, metal staple delivery instrument, and bone stapler.

Post-operative care

Following the procedure (performed arthroscopically or ‘mini-open’ approach), standard pain management measures should be undertaken. The Applicant stated that the postoperative protocol is immediate range of motion as tolerated, with the patient using a sling for comfort. Strengthening can begin once full range of motion has returned.

Specifically, post-operative care in Bokor et al. for patients:

- with symptomatic PTRCTs (**Population 1**) was: discontinuation of the sling when comfortable (maximum of 1 week); progress from passive-assisted to active motion (under physiotherapy supervision), with no restrictions on arm for 6 weeks (2); and
- with symptomatic FTRCTs (**Population 2**) a more extensive rehabilitation program was followed: discontinuation of sling during first six weeks; passive-assisted motion for six weeks and progression to active motion beyond six weeks; and after 12 weeks, a gradual resistance program was adopted (1).

PASC noted that one of the clinical claims of the submission is that the use of the implant leads to an earlier improvement of shoulder function compared with standard surgical repair. According to one of the clinical experts supporting the applicant, the recovery time after surgery with the implant is around six to eight weeks, whereas it is six months or more with standard surgery.

Access

The Applicant stated there are no current limitations on provision of the proposed medical service, with respect to accessibility.

PASC noted that accessibility to the proposed intervention in regional areas is not an issue, as all surgeons performing arthroscopic shoulder surgery should be able to perform the procedure after a short training course.

Prosthesis

The bovine bioinductive collagen implant is made from highly purified type I bovine collagen and engineered into a highly orientated, highly porous (85-90% porosity) scaffold that once is hydrated is approximately 2mm thick (36). The prosthesis is not designed to provide structural support immediately after surgery and absorbs within six months (36). It is attached under a slight amount of tension to assure good contact with the underlying tendon (1). The staples attaching the bovine BCI to the tendon (polylactic acid (PLA) staples, attached anteriorly, posteriorly and medially) and bone (polyether ether ketone (PEEK) staples, attached laterally) are designed to absorb within approximately 12 months (1, 2). In Bokor et al. (1, 2) the implant size was selected to cover almost the entire width of the repaired supraspinatus tendon in repairs of patients with symptomatic PTRCT (**Population 1**) or symptomatic FTRCT (**Population 2**).

Regulatory information

The medical device (bovine bioinductive collagen implant) is classified as a Class III medical device as per the TGA.

Bovine bioinductive collagen implant is listed on the Australian Register of Therapeutic Goods (ARTG) for the management and protection of rotator cuff tendon injuries where there has been no substantial loss of tissue:

- ARTG identifier 340095 (ARTG start date 24/07/2020)
- ARTG identifier 340096 (ARTG start date 24/07/2020)
- ARTG identifier 384118 (ARTG start date 16/02/2022)

PASC noted that since the previous submission in 2019, the REGENETEN bioinductive implant for the repair of rotator cuff tears has been approved by the TGA and listed on the Australian Register of Therapeutic Goods.

Comparator(s)

Standard surgical repair (i.e. without use of bovine bioinductive collagen implant) is the Applicant's nominated comparator.

Population 1

The Applicant proposed that use of bovine BCI would be provided in addition (i.e. add on service) to debridement and bursectomy.

The surgical options for symptomatic PTRCTs are non-repair surgery, or debridement⁴ (i.e. smooth the tendon tear), and surgical repair. These procedures may be carried out alone or together, and should always be performed arthroscopically (3). However, patients with symptomatic PTRCTs typically are expected to require standard repair surgery, using sutures or anchors.

Specifically, the Applicant stated that standard surgical treatment for PTRCTs has evolved from simple arthroscopic debridement to surgical repair procedures, of which there are two techniques:

- Trans-tendon repair; and
- Take-down and repair (6).

The trans-tendon repair involves maintaining the intact lateral portion of the tendon while repairing the medial aspect of the tendon. Following this, standard rotator cuff repair is performed using anchors and sutures. Theoretical benefits of a trans-tendon repair include anatomic restoration of the footprint and maintenance of the normal intact lateral cuff, which may improve biological or biomechanical characteristics and enhance healing (37).

The take-down and repair procedure involves artificially completing the tear during the surgery followed by standard rotator cuff repair using anchors and sutures (37). Although some surgeons advocate this technique, there is a reported failure rate of up to 18% (36). In addition, post-operative care is typically longer with this method (relative to trans-tendon technique) and may include six weeks of shoulder immobilisation (e.g. in sling) and rehabilitation over six months (36).

Specifically, for patients with articular-sided PTRCT, it is suggested both standard surgical repair procedures should be considered when the tear depth > 50% tendon thickness (6) (or Grade III according to Ellman).

The *I.S.Mu.L.T 'Rotator Cuff Tear Guidelines'* state that arthroscopic debridement with or without acromioplasty, and the surgical repair techniques (transtendinous or "completion and repair [i.e. take-down and repair]" technique) are the most frequent treatments for PTRCTs. However, these Guidelines advise that current evidence is low level, which does not allow determination of best treatment (19).

For application 1711 which assessed a different population, the definition for conservative management was called 'continued active conservative therapy' (1711 PSD).

Under the current and proposed clinical management algorithm in this application, patients that fail 3 months of conservative management can choose to either receive surgery or not. Although not indicated

⁴ Non-surgical repair or debridement includes several procedures: acromioplasty, subacromial bursectomy, smoothing of tendon lesions, excision of the coraco-acromial ligament, tenotomy or tenodesis of the long head of the biceps brachii, and procedures on the acromioclavicular joint (Beaudreuil 2010) (3)

in the current treatment algorithm, patients who may not be eligible for surgery or may have a preference to not have surgery would have continued conservative management.

PASC noted that MSAC Executive had sought advice on whether continued conservative management may be an additional comparator due to the intervention being used without standard surgical repair in subpopulation 1 (PTRCT).

The question of whether continued conservative management may be an additional comparator may be best assessed by considering which intervention (surgical repair or conservative management) the proposed intervention (use of bovine BCI) is most likely to replace in the clinical management pathway.

PASC noted the natural history of rotator cuff tears, where there is a proportion of patients who delay surgery but then get better. Furthermore, one of the clinical experts supporting the applicant explained that the introduction of the implant may lead to a differing and in particular a lower burden of rehabilitation after surgery. PASC considered that this might reduce the threshold for surgery for rotator cuff tears in Population 1 and therefore result in some share of patients who might otherwise have continued with conservative management opting for surgery instead. Therefore, PASC noted that it is still important to compare the intervention group to a natural history group.

PASC noted that one of the clinical experts supporting the applicant did not regard continued conservative management as a valid comparator, explaining that the proposed population is patients who have decided they need surgery as they have failed conservative treatment and therefore by implication those patients who continue with conservative management have already selected themselves out of this group. Including continued conservative management as a comparator would require changing the algorithm of current management of rotator cuff disease. PASC noted that the clinical expert also explained that in his opinion, the main obstacle to surgery for some patients was their fear of anaesthetics and this would not change even with a less onerous post-operative rehabilitation after surgery as facilitated by the bioinductive implant. It was also explained that of those PTRCT patients who do not improve after initial conservative treatment, some (unless there is evidence to support many- this comment will reflect the referral bias of surgeons) 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. A representative of the applicant also questioned whether a trial comparing the use of the implant with a conservative arm would be ethical in this population.

PASC emphasised that if there is clinical equipoise, randomised controlled trials in surgery are not only justified ethically but also required. PASC noted that in a recent Cochrane review comparing repair with no repair of rotator cuff tears, the authors found no evidence of different outcomes in one year across a wide range of measures and concluded that more randomised controlled studies are required, including sham and placebo surgery.

PASC queried whether the size of the tear (in PTRCT) may determine whether a patient may continue with continued conservative management rather than choosing a surgical option. The applicant's expert clarified that the decision for surgery was typically based on the degree of the patient's symptomatology rather than a specific cut-off point in terms of rotator cuff tear size, noting approximately 20% of patients typically respond to conservative management.

PASC stated given the considerations above including the prospect that introduction of the implant may reduce the threshold for surgery among patients who currently opt for continued conservative management due to the lower burden of rehabilitation post-surgery, there is enough justification to advise the applicant to include conservative management as additional comparator in Population 1.

Population 2

The Applicant proposed that the use of bovine BCI would be in addition (i.e. add-on service) to surgical repair for symptomatic FTRCTs, which require the use of standard sutures or anchors.

Standard surgical treatment for symptomatic FTRCTs is performed arthroscopically or as 'mini-open' surgery, and involves reattaching the muscle to the bone using standard sutures or anchors.

Prognostic factors, identified from case-series studies, have indicated the following outcomes following FTRCT surgery:

- Univariable analyses: Higher rate of secondary tearing AND/OR poorer clinical outcomes after repair by arthroscopy or open surgery are associated with the following:
 - Extent of tear (extension to infraspinatus muscle);
 - Tendon retraction;
 - Decrease in pre-operative subacromial height on X-ray;
 - Extensive fatty degeneration (assessed by computed tomography (CT) scan); and
 - Occupation.
- Multivariable analyses: Main negative prognostic factors for direct open repair of FTRCTs are long standing pre-operative signs, poor general health, former or current smoker (>40 pack-years) and a large tear ($\geq 5\text{cm}^2$) found during the procedure. Furthermore a tear of the subscapularis can be a negative prognostic factor for postoperative recovery (3).

Suturing

All rotator cuff tears (arthroscopic or mini-open) are surgically repaired with standard sutures or anchors. There are several techniques:

- Single-row: most common technique but reported high, up to 90% failure rates in case of large and massive injuries; and
- Double-row⁵: more resistant than single-row, but will impart greater strain on repaired tendon (19).

A 2013 meta-analysis of randomised controlled trials showed similar rates of re-tear using single- and double-row suture techniques (38).

Existing MBS items for standard surgical repair

The Applicant stated that standard surgical repair for both populations is currently claimed on the MBS using items 48960, 48906, and 48909 (Table 4). In addition, MBS items for anaesthesia and surgical assistants may be co-claimed with the items for surgical repair of the rotator cuff.

⁵ Double-row techniques increase costs in terms of materials and time of the operating room (Olivia 2015) (26)
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Table 4 Existing MBS items associated with standard surgical repair of the shoulder

Category 3 –Therapeutic Procedures Subgroup 15 – Orthopaedic
<p>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 Multiple Operation Rule (Anaes.) (Assist.) Fee: \$1,031.10 Benefit: 75% = \$773.35</p>
Category 3 –Therapeutic Procedures Subgroup 15 – Orthopaedic
<p>48906 SHOULDER, repair of rotator cuff, including excision of coraco-acromial ligament or removal of calcium deposit from cuff, or both – not being a service associated with a service to which item 48900 applies Multiple Operation Rule (Anaes.) (Assist.) Fee: \$618.65 Benefit: 75% = \$464.00</p>
Category 3 –Therapeutic Procedures Subgroup 15 – Orthopaedic
<p>48909 SHOULDER, repair of rotator cuff, including decompression of subacromial space by acromioplasty, excision of coraco-acromial ligament and distal clavicle, or any combination, not being a service associated with a service to which item 48903 applies Multiple Operation Rule (Anaes.) (Assist.) Fee: \$825.00 Benefit: 75% = \$618.75</p>

Source: MBS online, Medicare Benefits Schedule (39)

It was noted that MBS item 48960 is not specific to rotator cuff repair. This item also includes shoulder reconstruction, resection and replacement. In addition, this MBS item does not describe the severity of the rotator cuff tear (partial or full-thickness), and does not specify an age criteria or other clinical requirements in respect of prior treatments (e.g. failure of conservative management) that would apply to proposed use of bovine BCI in conjunction with surgical repair of rotator cuff tears.

MBS utilisation data (over the last four financial years) for the nominated MBS items are provided in Figure 2). The majority (>50%) of MBS use for standard surgical repair is claimed through item 48960.

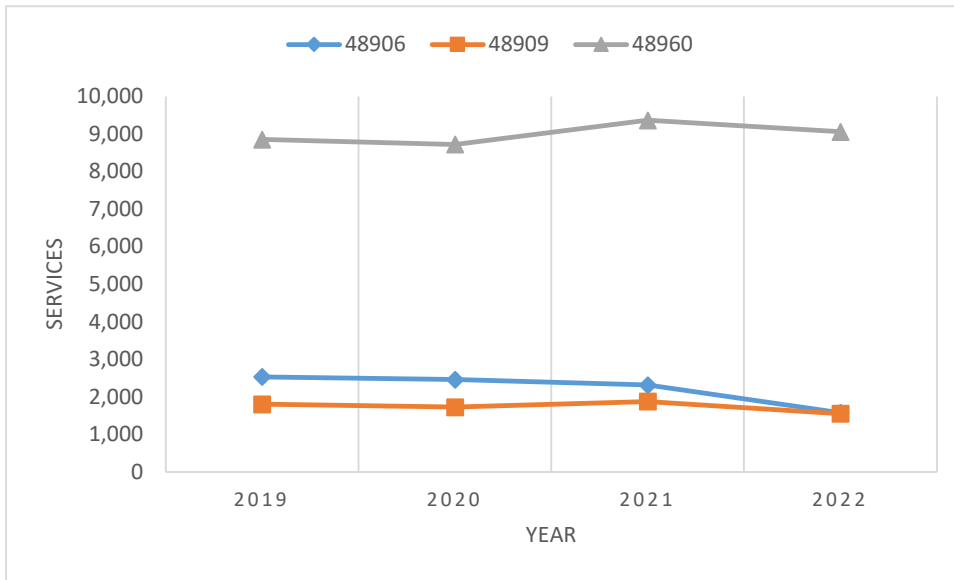


Figure 2 Recent MBS utilisation for nominated items that include standard surgery for rotator cuff repair

Source: Application Form, pp17-18 (verified to be correct accessing http://medicarestatistics.humanservices.gov.au/statistics/mbs_item.jsp (40)

MBS = Medicare Benefits Schedule

Outcomes

Safety

- Adverse events
- Procedural complications
- Longer-term adverse events
- Revision surgery

Clinical effectiveness

Functional outcomes

- American Shoulder and Elbow Surgeons standardized Form for the Assessment of the Shoulder (ASES)
- Constant-Murley shoulder score
- Oxford Shoulder Score (OSS)
- Visual Analogue Scale (VAS) pain
- Post-operative physical therapy
- Post-operative return to activities
- Single Assessment Numeric Evaluation (SANE)
- Progression to full-thickness tear (Population1 only: Patients with symptomatic partial-thickness rotator cuff tear)
- Western Ontario Rotator Cuff (WORC) index
- Quality of Life
 - EuroQol-five dimension scale (EQ-5D)
 - Short Form-36 Health Survey (SF-36)

Secondary effectiveness outcomes

- Length of hospital stay
- Time to return to work
- Opioid Consumption

Imaging-based outcomes

- Tendon thickness
- Size of the cuff defect (tear size, re-tear rate)

Cost-effectiveness

- Resource utilisation (surgical costs, diagnostic test, follow-up physiotherapy rehabilitation, pain management medication, and indirect costs (e.g. work days lost)
- Cost per life year gained, cost per quality-adjusted life year (QALY) gained, and incremental cost-effectiveness ratio.

Financial implications

- Total cost to Medicare Benefits Schedule and Australian Government budgets.
- Total projected annual PL benefits claimed and total out of pocket costs.

The applicant has made some changes to the proposed outcomes in this renewed application. Shoulder Pain and Disability Index (SPADI) and Shoulder pain were removed but VAS pain and Western Ontario Rotator Cuff (WORC) index have been added.

PASC noted that various patient reported outcome measures (PROMs) are used in different jurisdictions. Methodological research indicates that they are generally comparable. Hence, PASC noted the submission should not limit the PROMs assessed, but all available evidence should be used, to get as much data as possible on quality of life given its importance in this condition with the implication that the PROMs that the applicant has proposed to remove should be reinstated under 'Outcomes'.

Regarding the listing of imaging-based outcomes, the applicant has not made any comments on how these should be considered or provided any further definitions. As per MSAC Guidelines, surrogate or intermediate outcomes are acceptable if they have been validated as being able to predict patient-relevant outcome.

In the 1593 PSD for the previous submission, 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. 2014⁶), 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.

⁶ 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.

PASC noted the importance of assessing the effectiveness of REGENETEN in terms of functional outcomes, which are most important to patients, while there is no evidence to support correlating radiological outcomes to patient reported outcomes or to predict a reduced rate of osteoarthritis.

The applicant explained that its justification for adding opioid consumption as an outcome is that it is considered problematic in some countries and is also reported as an outcome in an ongoing randomised controlled trial pertaining to Population 1. Therefore, PASC considered that the applicant's addition of 'opioid use' as an outcome in the PICO is justified.

Clinical management algorithms

The current and proposed clinical management algorithm for identified population is provided in

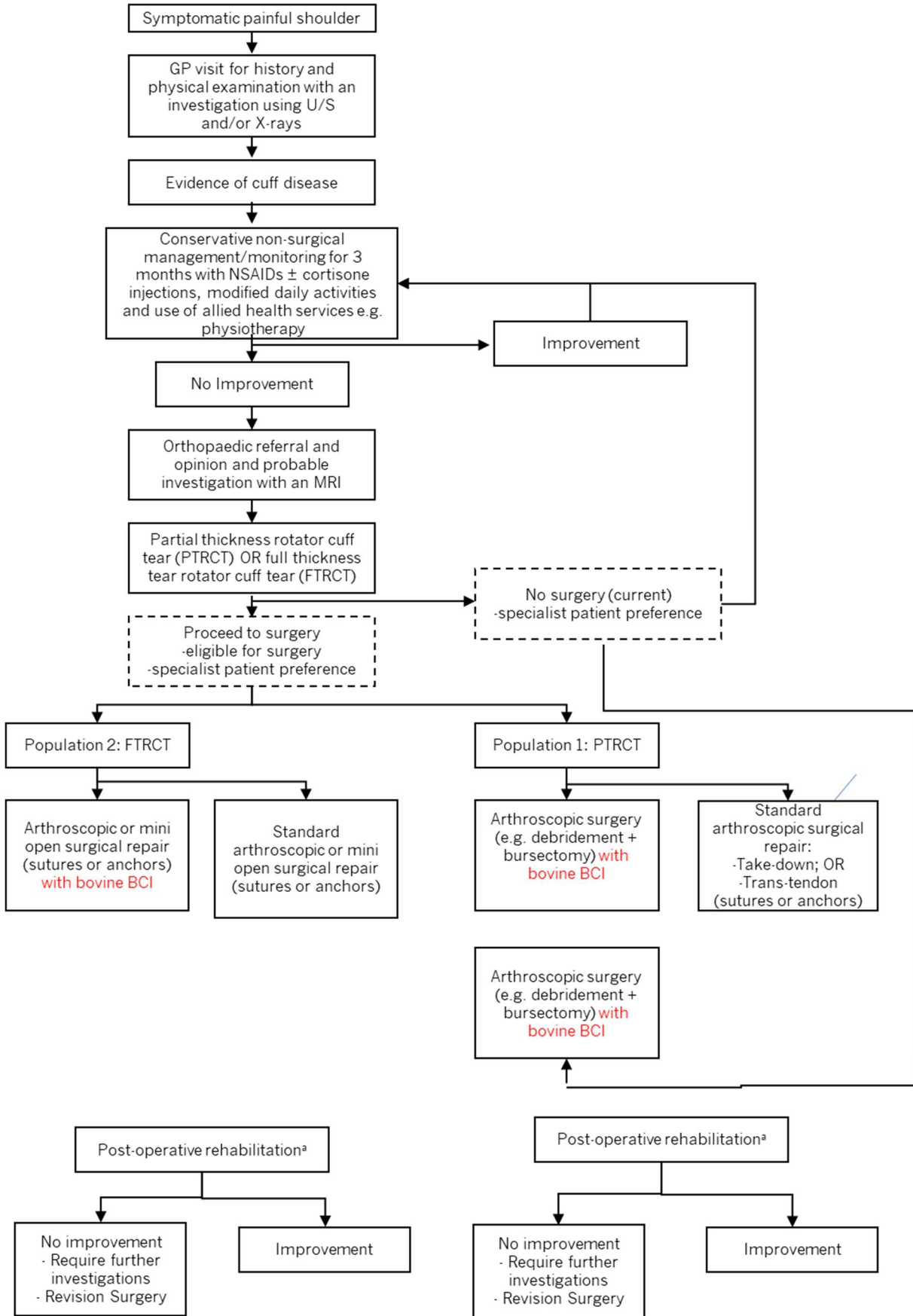


Figure 3.

The place of bovine BCI, performed in addition to arthroscopic surgery (debridement and bursectomy) in subpopulation 1 and in addition to standard arthroscopic or mini-open surgical repair in subpopulation 2 is highlighted in red.

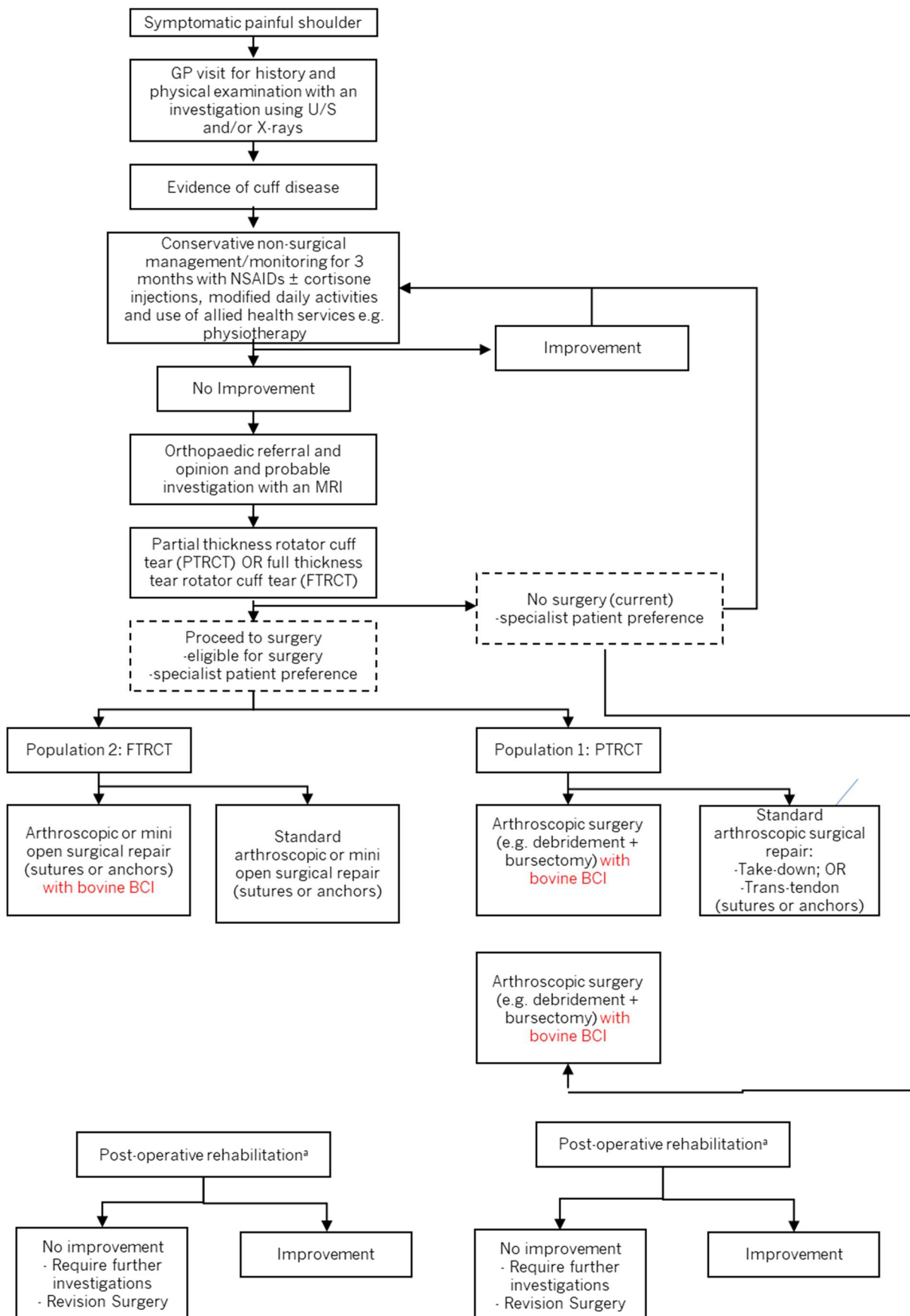


Figure 3 Current and proposed algorithm for Population 1 (PTRCT) and Population 2 (FTRCT)

BCI = bioinductive collagen implant; MRI = magnetic resonance imaging; NSAID = nonsteroidal anti-inflammatory drugs; U/S = ultrasound

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

A key difference between the intervention and comparator in **Population 1** is that bovine BCI can be used without standard repair techniques using sutures or anchors.

PASC noted the difference in post-operative rehabilitation between the intervention and comparator, with a claimed shorter recovery time when using the implant (six to eight weeks) compared with standard surgery (six months or longer).

The Applicant stated that after receiving surgery, patients are followed up for 3 months, as routine practice. Downstream services such as post-operative rehabilitation includes services associated with diagnostic imaging (X-ray and/or ultrasound and/or MRI), physical therapy sessions from physiotherapists and treatments for pain management (NSAIDs ± corticosteroid injections). The usual care for patients with a PTRCT is MRI (at diagnosis) and follow-up MRI, regardless of tear status.

The Applicant stated that following standard surgical repair (in either population), a repeat procedure (e.g. revision surgery) may be performed under the discretion of the surgeon if the repair was considered to have failed. The Applicant advised that repeat surgery is unlikely, as REGENETEN is unlikely to succeed on a second attempt, if it has already failed. In these patients, anatomic or reverse total shoulder replacement may be an option, if the clinician and patient choose and agree on that route.

It was noted that following surgical repair with bovine BCI failure in Thon et al. 2019 (25), failure was defined as “any implant-related adverse event, any failure of the implant itself, noted complications attributed to the implant, or any implant-related tissue reaction during the study period”. Secondary treatment failure was a lack of healing on either imaging modality (ultrasound and/or MRI) or the need for additional surgical procedures to be performed on the same shoulder during the study period, including conversion to reverse total shoulder arthroplasty.

PASC noted that the use of the REGENETEN implant would be a once only treatment.

Proposed economic evaluation

The overall clinical claim is that REGENETEN is associated with superior health outcomes for patients with RCTs through improved efficacy and at least non-inferior safety, if not superior safety, in comparison to treatment with standard surgical repair.

Supportive evidence for this claim includes three new ongoing randomised controlled trials for which no publications are yet available, one economic analysis (41), four registries, one review and 11 case series.

Data from the REGENETEN clinical trial program demonstrated that patients in the REGENETEN arm experienced significantly lower re-tear rates, significantly lower failure rate at the musculotendinous junction, lower post-operative fatty infiltration, no difference in complications between groups, improvement in function and pain scores (Constant-Murley Shoulder Score and VAS pain score assessments) compared to the control group (standard surgical repair) (Ferreira Barros, 2022; Iban, 2022).

Based on this clinical claim of superior clinical effectiveness and non-inferior safety of REGENETEN bioinductive implant for the repair of rotator cuff tear, compared to standard arthroscopic surgical repair, the appropriate economic evaluation is a cost-effectiveness or cost-utility analysis (Table 5).

PASC noted that given the clinical claim of superior comparative effectiveness and non-inferior safety the appropriate economic evaluation is a cost-effectiveness or cost-utility analysis.

PASC noted that an evaluation in terms of cost per life years gained would not be meaningful as there are no mortality implications associated with rotator cuff pathology. The applicant confirmed they plan to undertake a cost-utility analysis to consider cost per quality-adjusted life years as the outcome.

Table 5 Classification of comparative effectiveness and safety of the proposed intervention, compared with its main comparator, and guide to the suitable type of economic evaluation

Comparative safety	Comparative effectiveness			
	Inferior	Uncertain ^a	Noninferior ^b	Superior
Inferior	Health forgone: need other supportive factors	Health forgone possible: need other supportive factors	Health forgone: need other supportive factors	? Likely CUA
Uncertain ^a	Health forgone possible: need other supportive factors	?	?	? Likely CEA/CUA
Noninferior ^b	Health forgone: need other supportive factors	?	CMA	CEA/CUA
Superior	? Likely CUA	? Likely CEA/CUA	CEA/CUA	CEA/CUA

CEA=cost-effectiveness analysis; CMA=cost-minimisation analysis; CUA=cost-utility analysis

? = reflect uncertainties and any identified health trade-offs in the economic evaluation, as a minimum in a cost-consequences analysis

^a 'Uncertainty' covers concepts such as inadequate minimisation of important sources of bias, lack of statistical significance in an underpowered trial, detecting clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or the comparative safety considerations

^b An adequate assessment of 'noninferiority' is the preferred basis for demonstrating equivalence

Proposal for public funding

This application is linked to a co-dependent Medical Devices and Human Tissue Advisory Committee (MDHTAC) application for listing bovine BCI (used in surgical repair of rotator cuff tears) on the Prescribed List of Medical Devices and Human Tissue Products (PL) (with the prosthesis to be used in conjunction with existing MBS items). No new MBS item was requested by the Applicant.

Costing information of the intervention for the assessment

The Applicant provided the breakdown of estimated procedure costs associated with arthroscopic implantation of bovine BCI for the treatment of rotator cuff repair (Table 6).

Table 6 Cost of bovine BCI, applied arthroscopically, in surgical repair of rotator cuff tears

Row	Component	Cost/ MBS fee	Cost/MBS hospital rebate (75%)	Source/calculation
A	Prescribed List of Medical Devices and Human Tissue Products	\$Redacted	\$Redacted	Applicant
B	Pre-anaesthesia consultation	\$47.80	\$40.65	MBS item 17610
C	Initiation anaesthesia	\$108.50	\$81.40	MBS item 21622
D	Arthroscopic (or mini-open) ^a surgery including application of BCI	\$1, 031.10	\$773.35	MBS item 48960
E	Anaesthesia (10 minutes) ^b required for application of bovine BCI in population 1 (phase 3) and population 2 (phase 4)	\$21.70	\$16.30	MBS item 23010
F	Surgical assistant	\$206.22	\$154.67	MBS item 51303
G	Total	\$Redacted	\$Redacted	Sum (A: F)

Source: attachment to Application Form

BCI = bioinductive collagen implant; MBS = Medicare Benefits Schedule;

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

^b Applicant advised that the estimated time of the procedure is 15-30 minutes

The Applicant advised that surgery with use of bovine BCI would be claimed on the MBS using items that relate to surgical repair of rotator cuff tears. The Applicant specified three MBS item descriptors (MBS items 48960, 48906 and 48909; see Table 4) that would apply to the proposed intervention. MBS item 48960 refers to arthroscopic repair.

These three items cannot be co-claimed.

Although 'mini-open' and arthroscopic rotator cuff surgical repair techniques attract the same MBS fee (included in MBS item 48960), the *I.S.Mu.L.T Guidelines* indicate that arthroscopy is more expensive and requires more operative time than the 'mini-open' technique (19). In the assessment phase, if data was available for operating room time in patients treated with arthroscopic vs. mini-open techniques in population 2, this could be incorporated in the assessment of cost-effectiveness (however, noting this inclusion is not critical as it would not be expected to be driving incremental differences in assessment of cost-effectiveness).

PASC noted the purpose of the application is for a listing on the Prescribed List of Medical Devices and Human Tissue Products (PL) – formerly the Prostheses List - not for a new MBS item number. Several existing MBS item numbers would be utilised if the procedures was deemed suitable for a patient.

PASC noted that MBS items 48960, 48906 and 48909 are suitable for this procedure, and noted item 48960 is the most applicable item as it refers to arthroscopic repair.

PASC noted that MBS item 48918 is not appropriate for REGENETEN and has been removed from the submission.

Summary of public consultation input

PASC noted and welcomed consultation input from 1 organisation and 5 individuals, all of whom were health professionals (medical specialists). The 1 organisation that submitted input was:

- Private Healthcare Australia (PHA)

With the exception of Private Healthcare Australia (PHA) who were not supportive, the consultation feedback received was all supportive of public funding for Bioinductive Implant for the repair of rotator cuff tear (REGENETEN). PHA raised a number of concerns, predominately in relation to insufficient evidence that the device is effective and the cost to private health insurers.

Clinical need and public health significance

The main benefits of public funding received in the individual consultation feedback included better healing rates, quicker recovery and return of function and improved tendon quality reducing revision rate. Most of the individuals stated that REGENETEN is an excellent prosthesis with improved outcomes that would strongly benefit the community and expressed frustration that not all patients have the financial means to access it. Private Healthcare Australia (PHA) see no benefit without a high-quality independent study that is not conducted by consultant surgeons to the sponsor.

The clinical disadvantages of public funding received in the consultation feedback was in relation to the cost of the device. One individual noted that the cost versus outcomes metrics need to be evaluated. PHA stated that the device is clinically unproven and patients may undertake surgery that they would not otherwise have had due to the marketing and promotion of the device.

Other services identified in the consultation feedback as being needed to be delivered before or after the intervention included routine post operative management, physiotherapy, and imaging to examine healing.

Indication(s) for the proposed medical service and clinical claim

The consultation feedback from the five individuals ranged from agreeing to strongly agreeing with the proposed population(s). PHA strongly disagreed with the population stating it was broad and ill defined.

The consultation feedback ranged from strongly disagreeing to strongly agreeing with the proposed comparator(s). PHA stated that much of the partial thickness cohort would not advance to surgery and the comparator should be no cost.

The consultation feedback ranged from strongly disagreeing to strongly agreeing with the clinical claim. An individual noted there is no similar product available and several individuals stated that the proposed clinical claims and benefits have been replicated in patients treated over the years. PHA stated that the clinical claim is difficult to assess due to limited low-level evidence.

Cost information for the proposed medical service

The consultation feedback from the individuals agreed with the proposed service descriptor and noted that no service fee was provided for consultation. PHA noted there is no service descriptor as the service is covered under existing MBS items and only a Prescribed List listing is sought but the cost for this listing is not provided. PHA considered listing of the device would increase costs to consumers through device costs, hospital costs and medical rebates, result in a substantial increase in government spend via MBS and the Private Health Insurance Rebate.

PASC noted that Private Healthcare Australia submitted organisation feedback that raised concerns around a significant increase in costs to government and private health insurers from the listing of REGENETEN. The submission also raised concerns that many people would opt for this procedure despite the lack of much additional evidence being presented since the previous submission.

PASC noted the applicant had provided a response to the Private Healthcare Australia consultation feedback arguing that its claims about the higher cost to government was not reflective of the MBS item numbers being claimed for the application.

PASC noted that five specialists also provided their feedback, four of whom were supportive, and one of them was more neutral.

Next steps

PASC noted the applicant has elected to progress its application as an ADAR (Applicant Developed Assessment Report).

Applicant comment on the ratified PICO Confirmation

Smith+Nephew (S+N) consider references to MSAC Application 1711 – Review of MBS items for subacromial decompression (SAD) does not include rotator cuff repair and has no connection to the PICO presented in this application.

We would like it duly noted that S+N was not supported by MSAC in 2020 and MSAC requested high quality evidence before resubmitting; at that time the comparator was agreed to be standard surgical repair. As such S+N facilitated multiple Randomised Control Trials and presented this in our Application

1593.1 to be reviewed. We were surprised to note PASC's proposed inclusion of CMM as a comparator for Population 1 after 3 years of RCTs, comparative studies, and independent research into RCR standard of care globally compared to RCR with REGENETEN. S+N are compliant and committed to the Australian reimbursement process, however, we do not support PASC's addition of CMM as a comparator for Population 1.

S+N is aligned and appreciates PASC's acknowledgement that the time frame of a minimum of three months of conservative management is reasonable in our population definition given clinician advice and the high variability of this time period.

Our patient population are those who have experienced significant burden and impact to their quality of life as a result of the recalcitrant and symptomatic nature of their tear, and upon failing CMM continue to have persistent symptoms, have requested further intervention via surgical means. This patient population is very specific, highly refined to patients that have shown no benefit from CMM.

S+N want to clarify a comment made in this ratified PICO, "*PASC noted the advice from one of the clinical experts supporting the applicant that the intervention is not a less invasive option to standard surgical repair.*" This statement cannot be generalised to both populations, rather:

- In population 1, REGENETEN tendon repair is a less invasive option to standard surgical repair.
- In population 2, REGENETEN tendon repair is not a less invasive option to standard surgical repair.

S+N want to clarify that although no certification or additional training is required to implant REGENETEN, S+N provides product training and in theatre support to surgeons in both city and regional locations throughout Australia.

S+N would like to address the misalignment regarding the inclusion of CMM as an additional comparator for population 1. When we submitted our initial application to MSAC in 2019, there was no mention or discussion of including CMM as a comparator for either population throughout the entire MSAC process. The primary feedback we received from MSAC pertained to the limited evidence supporting REGENETEN. Consequently, in response to MSAC's recommendations in the Ratified PSD, S+N made substantial investments in head-to-head randomised controlled trials involving the agreed population and comparator, which were submitted in application 1593.1 in 2023.

MSAC Executive advised only a focused approach is required to define duration of failure and whether continued conservative management may be an additional comparator due to the intervention being used without standard surgical repair in population 1. PASC was asked to confirm that continued conservative management is not a relevant additional comparator, due to it being unlikely that patients eligible for surgical repair would continue with a failed non-surgical treatment option; a notion that S+N concur with.

It is a matter of concern for us that PASC has chosen to modify the agreed comparator, despite the fact that the PICO submitted in March 2023 closely mirrors the previous submission, with near-identical parameters. We find this particularly inequitable.

There may be some misunderstanding with regards to how REGENETEN is used in population 1. Specifically, that "bovine BCI can be used without standard repair techniques using sutures or anchors"; this statement is not accurate. For clarity, the surgical repair of Population 1, the REGENETEN implant is fixed to the tendon defect and bony footprint using proprietary anchors supplied in the REGENETEN kit. In this case, a repair is performed via the bioinductive implant alone (i.e., no additional conventional suture anchors are needed in this procedure).

S+N agree that CMM is an effective first-line treatment for patients with symptomatic RCTs. However, when patients do fail CMM, they are at risk as tears progress and become more complicated to treat.

S+N acknowledge PASCs emphasis that a randomised controlled trial comparing REGENETEN to non-surgical intervention in both populations “are justified”, however, continue to contend this notion, as patients enrolling in our clinical trials typically present after 30 months of symptoms. Given this extensive attempt to resolve their symptoms with CMM, it is, therefore, unethical and inappropriate to randomise this small group of patients who continue to experience an ongoing and significant impact to their quality of life as a result of their pain to a no-surgery arm of a study. Furthermore, it is likely that ethics committees would not approve such a study design for implementation in Australia.

S+N acknowledge PASC’s commentary regarding the exclusion of the population specific limitations on the relevant MBS codes (48960, 48906 and 48909). It is important to note that the absence of the severity of the RCT, age criteria and other clinical requirements in MBS item 48960 is a limitation in the description of the service code that cannot be rectified by S+N with this application, as it is **not** the responsibility of the sponsor, nor is it the objective of this reimbursement submission.

The clinical management algorithm as presented by the PASC, implies that patients who are not seeking a surgical intervention, would then go on to receive arthroscopic surgery at some point in time. The clinical experts and S+N disagree because:

- It is not practical or feasible for a patient who is at one point opting for ‘no surgery’ to then receive arthroscopic or mini open surgery (with or without BCI); as was stated in the draft pre-PASC PICO Confirmation that it is unlikely that patients who would choose to continue with conservative management would opt to receive the proposed intervention.

S+N suggest that ‘no surgery’ be excluded from this algorithm, as these patients **are not included as part of our patient population**. Since the PASC meeting in August, S+N have progressed with the economic evaluation and found no data to support the translation of PROMS into QALYs to population 1. Therefore, the economic strategy for population 1 has been adjusted; we are instead progressing with a cost-effectiveness analysis for population 1, using PROMs as the health outcome.

S+N wish to highlight their disagreement with the comments made by PHA with respect to safety of the device, the levels of evidence, cost to consumers and the claim that REGENETEN was not clinically or cost effective. The 2023 application (1593.1) presents multiple high level RCT data, and MSAC will have full access to the extensive information set including a multicentre triple-blinded RCT yet to be released, exclusive to the upcoming ADAR.

S+N strongly disagree with PHA’s assumption that the population is ‘broad and ill defined’. S+N has stated that the first line of treatment for symptomatic RCT is conservative management. The requirement to have “failed” conservative management means that over 90% of patients are successfully treated with conservative measures and are thus removed from the rotator cuff repair (RCR) population each year. In a clear show of support, the five highly experienced shoulder specialists and the PASC are aligned with the defined patient population within the PICO.

PHA’s assumption that conservative medical management instead of surgical repair is “no cost” to the healthcare system is inaccurate and does not address the significant ongoing costs which are heavily born by the patient, the employer and the Australian Healthcare System.

It is clear from the 10 years of clinical experience utilising REGENETEN in Australia and the public consultation on this PICO, that the surgeon community believes that REGENETEN is a highly valued part of their armoury in the treatment of Rotator Cuff Repair.

Smith+Nephew wish to submit an ADAR in the February 2024 cycle and have notified the MSAC Secretariat via email of this intention on the 27th September 2023.

References

1. 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.
2. Bokor DJ, Sonnabend D, Deady L, Cass B, Young A, Van Kampen C, et al. Evidence of healing of partial-thickness rotator cuff tears following arthroscopic augmentation with a collagen implant: a 2-year MRI follow-up. 2016;6(1):16.
3. Beaudreuil J, Dhénain M, Coudane H, Mlika-Cabanne NJO, Surgery T, Research. Clinical practice guidelines for the surgical management of rotator cuff tears in adults. 2010;96(2):175-9.
4. Clark JJTJob, volume jsA. Tendons, ligaments, and capsule of the rotator cuff. Gross and microscopic anatomy. 1992;74(5):713-25.
5. New Zealand Guidelines Group. The diagnosis and management of soft tissue shoulder injuries and related disorders. New Zealand: Accident Compensation Corporation. New Zealand; 2004.
6. Bollier M, Shea KJTIOJ. Systematic review: what surgical technique provides the best outcome for symptomatic partial articular-sided rotator cuff tears? 2012;32:164.
7. Ellman HJCo, research r. Diagnosis and treatment of incomplete rotator cuff tears. 1990(254):64-74.
8. Matthewson G, Beach CJ, Nelson AA, Woodmass JM, Ono Y, Boorman RS, et al. Partial thickness rotator cuff tears: current concepts. 2015;2015.
9. Modi CS, Smith CD, Drew SJJjoss. Partial-thickness articular surface rotator cuff tears in patients over the age of 35: Etiology and intra-articular associations. 2012;6(1):15.
10. Sher JS, Uribe JW, Posada A, Murphy BJ, Zlatkin MBBJ. Abnormal findings on magnetic resonance images of asymptomatic shoulders. 1995;77(1):10-5.
11. Mall NA, Kim HM, Keener JD, Steger-May K, Teefey SA, Middleton WD, et al. Symptomatic progression of asymptomatic rotator cuff tears: a prospective study of clinical and sonographic variables. 2010;92(16):2623.
12. Lo IK, Burkhart SSJATJoA, Surgery R. Transtendon arthroscopic repair of partial-thickness, articular surface tears of the rotator cuff. 2004;20(2):214-20.
13. Tashjian RZJCism. Epidemiology, natural history, and indications for treatment of rotator cuff tears. 2012;31(4):589-604.
14. Washburn III R, Anderson TM, Tokish JMJA. Arthroscopic rotator cuff augmentation: surgical technique using bovine collagen bioinductive implant. 2017;6(2):e297-e301.
15. Sambandam SN, Khanna V, Gul A, Mounasamy VJWjoo. Rotator cuff tears: an evidence based approach. 2015;6(11):902.
16. Yamanaka K, Fukuda HJK. Pathological studies of the supraspinatus tendon with reference to incomplete thickness tear. 1987;11(1):98-102.
17. Denkers M, Pletsch K, Boorman R, Hollinshead R, Lo I, editors. Partial thickness rotator cuff tears: observe or operative. Proceedings of the American Academy of Orthopaedic Surgeons Annual Meeting; 2012.
18. DeOrio J, Cofield RJJBSA. Results of a second attempt at surgical repair of a failed initial. 1984;66:563-7.
19. Oliva F, Piccirilli E, Bossa M, Via AG, Colombo A, Chillemi C, et al. IS Mu. LT-rotator cuff tears guidelines. 2015;5(4):227.
20. Brun SJAFP. Shoulder injuries-management in general practice. 2012;41(4):188-94.
21. Shanahan EM, Sladek RJB, Rheumatology RC. Shoulder pain at the workplace. 2011;25(1):59-68.
22. Le BT, Wu XL, Lam PH, Murrell GAJTajom. Factors predicting rotator cuff retears: an analysis of 1000 consecutive rotator cuff repairs. 2014;42(5):1134-42.

23. Iannotti JP, Deutsch A, Green A, Rudicel S, Christensen J, Marraffino S, et al. Time to failure after rotator cuff repair: a prospective imaging study. 2013;95(11):965-71.
24. McElvany MD, McGoldrick E, Gee AO, Neradilek MB, Matsen III FAJTAjasm. Rotator cuff repair: published evidence on factors associated with repair integrity and clinical outcome. 2015;43(2):491-500.
25. Thon SG, O'Malley L, O'Brien MJ, Savoie III FHJTAjasm. Evaluation of Healing Rates and Safety With a Bioinductive Collagen Patch for Large and Massive Rotator Cuff Tears: 2-Year Safety and Clinical Outcomes. 2019:0363546519850795.
26. AIM. Appropriate Use Criteria: Joint Surgery. 2021 [Available from: https://aimspecialtyhealth.com/wp-content/uploads/2021/01/AIM_Guidelines_MSK_Joint-Surgery.pdf]
27. Abdul-Wahab TA, Betancourt JP, Hassan F, Thani SA, Choueiri H, Jain NB, et al. Initial treatment of complete rotator cuff tear and transition to surgical treatment: systematic review of the evidence. *Muscles Ligaments Tendons J.* 2016;6(1):35-47.
28. Dickinson RN, Ayers GD, Archer KR, Fan R, Page C, Higgins LD, et al. Physical therapy versus natural history in outcomes of rotator cuff tears: the Rotator Cuff Outcomes Workgroup (ROW) cohort study. *Journal of Shoulder and Elbow Surgery.* 2019;28(5):833-8.
29. Matsen FA TR, Wirth MA, Rockwood. In: *Rotator cuff. In the Shoulder.* THird ed. Philadelphia2004.
30. Neer CS, 2nd. Impingement lesions. *Clinical orthopaedics and related research.* 1983(173):70-7.
31. Yamaguchi K, Tetro AM, Blam O, Evanoff BA, Teefey SA, Middleton WDJJoS, et al. Natural history of asymptomatic rotator cuff tears: a longitudinal analysis of asymptomatic tears detected sonographically. 2001;10(3):199-203.
32. Paloneva J, Lepola V, Äärämaa V, Joukainen A, Ylinen J, Mattila VMJBmd. Increasing incidence of rotator cuff repairs—a nationwide registry study in Finland. 2015;16(1):189.
33. Personal communication. MSAC Application 1593 - Response from Applicant to Pre PASC Questions. In: Health Do, editor. Brisbane2019.
34. Morse K, Davis AD, Afra R, Kaye EK, Schepsis A, Voloshin IJTAjasm. Arthroscopic versus mini-open rotator cuff repair: a comprehensive review and meta-analysis. 2008;36(9):1824-8.
35. Huang R, Wang S, Wang Y, Qin X, Sun YJSr. Systematic review of all-arthroscopic versus mini-open repair of rotator cuff tears: A meta-analysis. 2016;6:22857.
36. Schlegel TF, Abrams JS, Bushnell BD, Brock JL, Ho CP. Radiologic and clinical evaluation of a bioabsorbable collagen implant to treat partial-thickness tears: a prospective multicenter study. *Journal of Shoulder and Elbow Surgery.* 2018;27(2):242-51.
37. Woods TC, Carroll MJ, Nelson AA, More KD, Berdusco R, Sohmer S, et al. Transtendon rotator-cuff repair of partial-thickness articular surface tears can lead to medial rotator-cuff failure. 2014;5:151.
38. Sheibani-Rad S, Giveans MR, Arnoczky SP, Bedi AJATJoA, Surgery R. Arthroscopic single-row versus double-row rotator cuff repair: a meta-analysis of the randomized clinical trials. 2013;29(2):343-8.
39. MBS. MBS Online. Medicare Benefits Schedule: Australian Government. Department of Health; 2019 [Available from: <http://www.mbsonline.gov.au/internet/mbsonline/publishing.nsf/Content/Home>].
40. Australian Government. Department of Human Services. Medicare Australia Statistics Canberra: Department of Human Services; 2019 [Available from: http://medicarestatistics.humanservices.gov.au/statistics/mbs_item.jsp].
41. McIntyre LF, Nherera LM, Schlegel TF. Resorbable Bioinductive Collagen Implant Is Cost Effective in the Treatment of Rotator Cuff Tears. *Arthrosc Sports Med Rehabil.* 2023;5(2):e367-e74.