MSAC Application 1593.2

Bioinductive implant for the repair of rotator cuff tear

PICO Set

Population

Describe the population in which the proposed health technology is intended to be used:
The population that relates to this application are patients who receive a REGENETEN™ bioinductive collagen implant (BCI) (Hereafter referred to as 'REGENETEN'), in addition to a mechanical surgical repair (full-thickness tears) of clinically diagnosed symptomatic rotator cuff tears. Specifically, patients with identified symptomatic full-thickness rotator cuff tear (FTRCT) where there is no substantial loss of tissue who have failed at least three months of conservative medical management (CMM).

Specify any characteristics of patients with the medical condition, or suspected of, who are proposed to be eligible for the proposed health technology, describing how a patient would be investigated, managed and referred within the Australian health care system in the lead up to being considered eligible for the technology:

The population that relates to the Prescribed List request are patients who receive a REGENETEN in addition to a surgical repair, who have symptomatic full-thickness rotator cuff tear rotator cuff tears of the shoulder. It is proposed that, in order to access this treatment, patients should 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 (e.g. physiotherapy) for at least three months. This was similar to the definition applied in the early feasibility Australian studies by Bokor et al. (1, 2).

The clinical workup includes documenting patient history and symptoms (mobility, stability, pain, strength) patient characteristics and biological factors that may affect healing (particularly age, smoking, diabetes, autoimmune disease, social and occupational context), and establishing the morphological features of the tear by physical examination and medical imaging (3).

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

Provide a rationale for the specifics of the eligible population:

The rotator cuff provides glenohumeral joint stability (3). It is a group of four muscles and their tendons (supraspinatus, infraspinatus, teres minor, and subscapularis) at the shoulder joint which form a multilayered horseshoe shape cuff around the head of the humorous bone (4). Each tendon has a separate footprint with a wide range of widths and lengths (range medial to lateral: 12-33mm; range anterior to posterior: 15-55mm; Table 1.

Table 1 - Rotator cuff tendon dimensions

Rotator cuff tendon	Medial to lateral width		Anterior to posterior width	
	Mean (mm)	Range (mm)	Mean (mm)	Range (mm)
Supraspinatus	16	12-20	23	18-33
Infraspinatus	18	12-24	28	20-45
Teres minor	21	10-33	29	20-40
Subscapularis	20	15-25	40	35-55

Source: Table 1 of Matthewson 2015 (5)

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 tears are degenerative

tears and are due to the progression of chronic tendonitis[1], which may or may not be symptomatic (3). However, rotator cuff tears that occur as a result of trauma, are rare in young patients (age<35 years) (6). 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.

FTRCTs can involve the full detachment of a length 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 (21), which classifies FTRCT as 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 (6).

The current Australian evidence base (Bokor et al (1, 2)) for REGENETEN is in patients with symptomatic [chronic shoulder pain ≥3months] medium (1-3cm) FTRCTs. However, it was noted in a recent US study (Thon et al 2019 (22)) that REGENETEN was applied to a population with more advanced disease severity: patients with symptomatic large and massive (>3cm and minimum 2-tendon involvement) FTRCTs (see Table 3 appendix). PASC queried the 3- month wait for the FTRCT population, as it would seem unlikely this population would wait 3 months before a surgical procedure. PASC confirmed this would be rare, but accepted the description should remain as is.

Intervention

Name of the proposed health technology:

REGENETEN Bioinductive Implant for the repair of rotator cuff tear

Describe the key components and clinical steps involved in delivering the proposed health technology:

The procedure is performed under general anaesthesia (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 (23, 24). 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 (25).

The Applicant advised, based on expert opinion and case study reference, that the average time to implant the REGENETEN system is 10 minutes (26) and depends on the learning curve of the surgeon. Upon receipt of final results which were not available at the time of Application 1593.1 submission, the duration of surgery for transosseous-equivalent full-thickness tendon repair with

[1] Note 'tendinitis' implies a pathology that is not strictly correct. Instead, one should use tendinosis, which is not an inflammatory disorder. Tendinosis (tendinitis) is caused by collagen fibre fatigue and usually develops from repetitive activity at, or above, shoulder height (NZGG 2004; 6)

REGENTEN is 90.5±19.9 minutes, whilst transosseous-equivalent full-thickness tendon repair without REGENETEN (i.e. standard of care) duration was 76.6±17.6 (p <0.0001); indicating an average incremental procedure time of 13.9 minutes (Ruiz Ibán et al., 2024) . This is because REGENETEN is implanted in phase 4 of the surgical repair procedure in addition to implanting suture anchors (as surgical repair with sutures or anchors is required in addition to REGENETEN). If surgical repair was performed, this was immediately prior to applying REGENETEN (D. J. Bokor et al., 2015; Thon et al., 2019).

The Applicant's summary of the phases required for surgery is provided in Table 2.

Table 2: Description of surgical procedures with use of REGENETEN

Phase	**FTRCT**	**Incremental Procedure time**
Phase 1	Anaesthesia and skin penetration	-
Phase 2	Debridement, diagnosis and bursectomy	-
Phase 3	Standard arthroscopic or mini-open surgical repair (Sutures or anchors)[a]	
Phase 4	Arthroscopic surgical repair with REGENETEN	13.9 minutes (Ruiz Ibán et al., 2024).

N/A = not applicable

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

The Applicant stated that the proposed intervention is intended to be performed once per shoulder per lifetime.

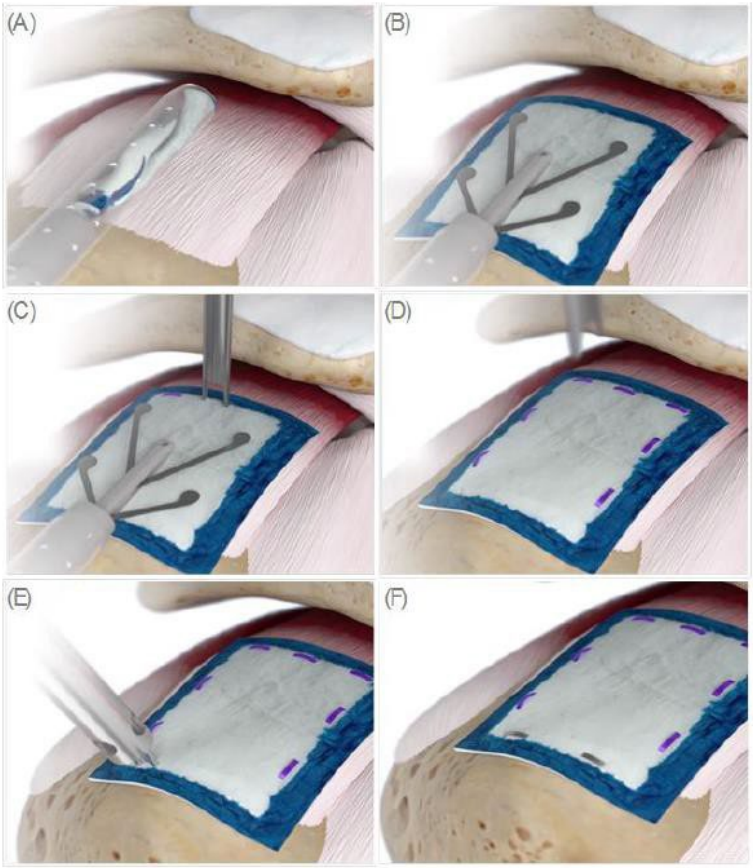
The procedure is performed by orthopaedic surgeons. *The Applicant and its nominated clinical expert confirmed at PASC that no additional training is required by orthopaedic surgeons to use REGENETEN in appropriate patients. However, this should be verified during the assessment phase.*

The Applicant also provided the detailed surgical steps in arthroscopic use of REGENETEN™ (as published in Wasburn et al. 2017 (17) 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. Determine the tendon width in millimeters (mm) using a suitable measuring instrument
6. Select a REGENETEN Bioinductive Implant size that is slightly smaller than the width of the tendon
7. Hydrate the REGENETEN (in sterile solution) for two minutes
8. The graft is loaded into the delivery instrument: After hydration, use the REGENETEN Bioinductive Implant Delivery Instrument and accessories to assist in positioning the scaffold over the tendon with one end overlapping the tendon insertion. Reference the REGENETEN Bioinductive Implant Delivery Instrument IFU.
9. The graft is introduced until the red button becomes prominent.
10. The graft is deployed. The REGENETEN Bioinductive Implant is secured to the tendon and bone. Ensuring that the device is in good contact with the tendon.
11. A second lateral cannula is placed just off the lateral edge of the acromion.

12. Soft-tissue staples are placed through the graft into the underlying rotator cuff.
13. The tendon markers are removed.
14. A bone stapler awl is used to tension the graft from the lateral portal.
15. The bone staples are placed.
16. The instruments are removed, and the wounds are closed in the standard fashion
17. Application of the REGENETEN Bioinductive Implant does not modify the postoperative treatment.

Figure 1 - Application of bovine BCI (using REGENTEN™)



Source: Applicant feedback (27)
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

Identify how the proposed technology achieves the intended patient outcomes:

The REGENETEN implant, when used as an adjunct to a mechanical repair (full-thickness tears), provides a porous scaffold for the formation of new tendon-like tissue. REGENETEN supports the body's natural healing response to facilitate new tendon-like tissue growth and change the course of rotator cuff tear progression. As the newly formed tissue begins to take up more local stress, a natural cell-based remodelling of the extracellular matrix occurs, and the implant is resorbed within six months (28). The load sharing abilities of the new tendon-like tissue decreases the strain in the native tendon to allow for tendon healing and functional gains (29). REGENETEN is positioned arthroscopically, tendon and bone staples secure the scaffold in place while the new

tissue is being generated. The procedure is performed under general anaesthesia and may be performed by mini-open surgery (30).

Does the proposed health technology include a registered trademark component with characteristics that distinguishes it from other similar health components?

Yes

Explain whether it is essential to have this trademark component or whether there would be other components that would be suitable:

The proposed medical service, REGENETEN™ Bioinductive Implant does include a registered trademark component, REGENETEN™, which is a bovine collagen implant available in Australia.

Are there any proposed limitations on the provision of the proposed health technology delivered to the patient (For example: accessibility, dosage, quantity, duration or frequency): (please highlight your response)

No

Provide details and explain:

There are no apparent constraints in the health care system that would impact on uptake.

There are no current limitations on provision of the proposed medical service, with respect to accessibility.

If applicable, advise which health professionals will be needed to provide the proposed health technology:

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

If applicable, advise whether delivery of the proposed health technology can be delegated to another health professional:

N/A

If applicable, advise if there are any limitations on which health professionals might provide a referral for the proposed health technology:

Referral to an orthopaedic surgeon for further review and possible surgical repair of the tear is indicated when symptoms fail to improve following a minimum of 3 months of conservative treatment and is impacting on comfort and function.

Is there specific training or qualifications required to provide or deliver the proposed service, and/or any accreditation requirements to support delivery of the health technology?

No

Provide details and explain:

N/A

Indicate the proposed setting(s) in which the proposed health technology will be delivered: (select all relevant settings)

☐ Consulting rooms
☒ Day surgery centre
☐ Emergency Department
☒ Inpatient private hospital
☒ Inpatient public hospital
☐ Laboratory
☐ Outpatient clinic
☐ Patient's home
☐ Point of care testing
☐ Residential aged care facility
☐ Other (please specify)

Specify further details here

Is the proposed health technology intended to be entirely rendered inside Australia?

Yes

Comparator

Nominate the appropriate comparator(s) for the proposed medical service (i.e. how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian health care system). This includes identifying health care resources that are needed to be delivered at the same time as the comparator service:

(please copy the below questions and complete for each comparator)

Please provide a name for your comparator:

Standard surgical repair (suture anchors fixation of tendon to bone, without use of REGENETEN).

Please provide an identifying number for your comparator (if applicable):

N/A

Please provide a rationale for why this is a comparator:

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 and anchors.

Simple arthroscopic debridement (with or without subacromial decompression) could be a comparator for some patients with symptomatic FTRCTs that are not amenable to direct repair. FTRCTs that are considered not amenable to direct repair are tears that are not reducible without tension or tears with > stage 2 fatty degeneration (3).

Prosthetic surgery (e.g. humeral prosthesis or a total reversed prosthesis) is also an option for patients with (index) shoulder with co-existing rotator cuff arthropathy (e.g. rotator cuff tear with joint disease, such as arthritis) and pseudo-paralytic symptoms due to a massive rotator cuff tear. However, a prosthesis is only indicated if all other treatment options have been exhausted (3).

Pattern of substitution – Will the proposed health technology wholly replace the proposed comparator, partially replace the proposed comparator, displace the proposed comparator or be used in combination with the proposed comparator? (please select your response)

☒ None *(used with the comparator)*
☐ Displaced *(comparator will likely be used following the proposed technology in some patients)*
☐ Partial *(in some cases, the proposed technology will replace the use of the comparator, but not in all cases)*
☐ Full *(subjects who receive the proposed intervention will not receive the comparator)*

Please outline and explain the extent to which the current comparator is expected to be substituted:

The Applicant has proposed that the use of REGENETEN 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:

- Univariate 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.
- Multivariate 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 (≥ 5cm2) 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-row[2]: more resistant than single-row but will impart greater strain on repaired tendon (25).

[2] Double-row techniques increase costs in terms of materials and time of the operating room (Olivia 2015) (26)

A 2013 meta-analysis of randomised controlled trials showed similar rates of re-tear using single- and double-row suture techniques (32).

Outcomes

(Please copy the below questions and complete for each outcome)

Overall

List the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be measured in assessing the clinical claim for the proposed medical service/technology (versus the comparator):

☒ Health benefits
☒ Health harms
☒ Resources

Outcome description – please include information about whether a change in patient management, or prognosis, occurs as a result of the test information:

Current treatment options for RCT include conservative and surgical repair (standard arthroscopic surgical repair) that do not address factors that lead to progression of degenerative disease. The introduction of REGENETEN to the RCT patient management algorithm will provide clinicians with an alternative or adjunct to standard arthroscopic surgical repair (sutures or anchors) that improves the quality of outcomes for patients with RCTs, whilst simultaneously reducing the economic burden to the health system and broader economy from lost productivity.

Using REGENETEN as an adjunct to the suture anchor repair has been shown to decrease the risk of retear following repair, therefore, minimising the number of surgical interventions required for rotator cuff pathology (35).

The introduction of REGENETEN, satisfies the following unmet needs:

- The need for a technology that can facilitate the formation of new tendon-like tissue and demonstrate a reduced risk of postoperative re-tears.
- Although radiographic re-tears is a surrogate outcome there is a large body of evidence which demonstrates it as having a level of clinical relevance.
- Systematic literature reviews with meta-analysis have shown statistically significant better ASES and CM scores in patients with healed tendon than those with retears within a wide follow-up range (1.5-10 years). This observation is highlighted in AAOS clinical practice guidelines which states that “healed rotator cuff repairs show improved patient reported outcomes to physical therapy and unhealed rotator cuff repairs”. When considering individual studies CM and ASES scores were consistently statistically significant better for patients with healed tendons when follow-up was greater than 2 years but comparable when less than 2 years. These observations are clearly highlighted in the findings of Kluger et al 2011 which reported no significant difference in patient reported outcomes between atraumatic re-tears and healed tears in the short term (3-6 months) but significant differences at 2 and 7 year follow-ups. The authors concluded “The parameters “recurrent tear” as well as “healed tendon” at 6 months postoperatively were predictors for the clinical outcomes at 7 years”. Therefore, the observations by Ruiz-Iban et al (2023) in not observing functional differences between patients who experienced a re-tear and did not at 1 year and the observations of significant differences at 2 years is not a surprise.
- Further to this, the study conducted by Ruiz-Iban et al is powered based on re-tear as an outcome. Patients who avoid a re-tear would not be expected to have differences in

functional outcomes, irrespective of their treatment arm. As a large proportion of patients avoided a re-tear in both study arms, the impact of REGENETEN on PROMs masks the benefit of REGENETEN and attention needs to be focused on a patient level and the impact that a failed surgery possess.

Outcomes

(Please copy the below questions and complete for each outcome)

Clinical Effectiveness Outcomes

List the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be measured in assessing the clinical claim for the proposed medical service/technology (versus the comparator):

☒ Health benefits
☐ Health harms
☒ Resources

Outcome description – please include information about whether a change in patient management, or prognosis, occurs as a result of the test information:

A change in patient management and prognosis is expected as a result of the test information.

Clinical Effectiveness Outcomes

Functional outcomes

- American Shoulder and Elbow Surgeons standardized Form for the Assessment of the Shoulder (ASES)
- Constant-Murley shoulder score
- Oxford Shoulder Score (OSS)
- VAS pain
- Single Assessment Numeric Evaluation (SANE)

Secondary effectiveness outcomes

List the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be measured in assessing the clinical claim for the proposed medical service/technology (versus the comparator):

☒ Health benefits
☐ Health harms
☒ Resources

Outcome description – please include information about whether a change in patient management, or prognosis, occurs as a result of the test information:

A change in patient management and prognosis is expected as a result of the test information.

Safety

List the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be measured in assessing the clinical claim for the proposed medical service/technology (versus the comparator):

☐ Health benefits
☒ Health harms
☒ Resources

Outcome description – please include information about whether a change in patient management, or prognosis, occurs as a result of the test information:

A change in patient management and prognosis is expected as a result of the test information.

Safety

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

Quality of Life

List the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be measured in assessing the clinical claim for the proposed medical service/technology (versus the comparator):

☒ Health benefits
☐ Health harms
☒ Resources

Outcome description – please include information about whether a change in patient management, or prognosis, occurs as a result of the test information:

A change in patient management and prognosis is expected as a result of the test information.

Quality of Life

- EuroQol-five dimension scale (EQ-5D)

Imaging-based outcomes

List the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be measured in assessing the clinical claim for the proposed medical service/technology (versus the comparator):

☒ Health benefits
☒ Health harms
☒ Resources

Outcome description – please include information about whether a change in patient management, or prognosis, occurs as a result of the test information:

A change in prognosis is expected as a result of the test information.

Imaging-based outcome

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

Cost-effectiveness

List the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be measured in assessing the clinical claim for the proposed medical service/technology (versus the comparator):

☒ Health benefits
☐ Health harms
☒ Resources

Outcome description – please include information about whether a change in patient management, or prognosis, occurs as a result of the test information:

A change in patient management and prognosis is expected as a result of the test information.

Cost-effectiveness

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

Financial implications

List the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be measured in assessing the clinical claim for the proposed medical service/technology (versus the comparator):

☒ Health benefits
☐ Health harms
☒ Resources

Outcome description – please include information about whether a change in patient management, or prognosis, occurs as a result of the test information:

A change in patient management is expected as a result of the test information.

Financial implications

- Total cost to Medicare Benefits Schedule and Australian Government budgets.

Claims

In terms of health outcomes (comparative benefits and harms), is the proposed technology claimed to be superior, non-inferior or inferior to the comparator(s)? (please select your response)

☒ Superior
☐ Non-inferior
☐ Inferior

Please state what the overall claim is, and provide a rationale:

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.

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, loser post-operative fatty infiltration, no difference in complications between groups (35).

Why would the requestor seek to use the proposed investigative technology rather than the comparator(s)?

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.

The results 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, loser post-operative fatty infiltration, no difference in complications between groups (35).

Identify how the proposed technology achieves the intended patient outcomes:

The REGENETEN implant, when used as an adjunct to a mechanical repair (full-thickness tears), provides a porous scaffold for the formation of new tendon-like tissue. REGENETEN supports the body's natural healing response to facilitate new tendon-like tissue growth and change the course of rotator cuff tear progression. As the newly formed tissue begins to take up more local stress, a natural cell-based remodelling of the extracellular matrix occurs, and the implant is resorbed within six months (28). The load sharing abilities of the new tendon-like tissue decreases the strain in the native tendon to allow for tendon healing and functional gains (29). REGENETEN is positioned arthroscopically, tendon and bone staples secure the scaffold in place while the new tissue is being generated. The procedure is performed under general anaesthesia and may be performed by mini-open surgery (30).

For some people, compared with the comparator(s), does the test information result in:

A change in clinical management?	Yes
A change in health outcome?	Yes
Other benefits?	Yes

Please provide a rationale, and information on other benefits if relevant:

Please refer to the above outcomes

In terms of the immediate costs of the proposed technology (and immediate cost consequences, such as procedural costs, testing costs etc.), is the proposed technology claimed to be more costly, the same cost or less costly than the comparator? (please select your response)

☒ More costly
☐ Same cost
☐ Less costly

Provide a brief rationale for the claim:

The Applicant advised that the comparative clinical claim is likely to be superior effectiveness for functional outcomes and similar safety. Therefore, a cost-effectiveness analysis or cost-utility analysis would be appropriate.

While adding to the overall surgical cost as an adjunct to standard rotator cuff repair, REGENETEN reduces the likelihood of a retear, which may lower the need for additional interventions in the long term.

Algorithms

Preparation for using the health technology

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, before patients would be eligible for the proposed health technology:

In order to access this treatment, patients should 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 (e.g. physiotherapy) for at least three months

Is there any expectation that the clinical management algorithm *before* the health technology is used will change due to the introduction of the proposed health technology?

No

Describe and explain any differences in the clinical management algorithm prior to the use of the proposed health technology vs. the comparator health technology:

N/A

Use of the health technology

Explain what other healthcare resources are used in conjunction with delivering the proposed health technology:

Increased procedure time to implant REGENTEN by 13.9 minutes

Explain what other healthcare resources are used in conjunction with the comparator health technology:

There are no other healthcare resources in conjunction to the standard repair techniques, using sutures or anchors.

Describe and explain any differences in the healthcare resources used in conjunction with the proposed health technology vs. the comparator health technology:

Healthcare system perspective:

A potential increase in hospital (operative) resources required with the application of REGENETEN in patients with symptomatic FTRCTs. The Applicant claimed that this is due to both intervention and comparator would receive standard arthroscopic or open rotator cuff surgery using sutures or anchors (phase 3 in this population) and the intervention arm would receive the additional 13.9 minutes application of REGENETEN surgical procedure, resulting in surgical time of 40-70 minutes vs. standard 30-60 minutes for standard surgical repair without REGENETEN (26, 27, 36) (see Table 5).

The duration of surgery for transosseous-equivalent full-thickness tendon repair with REGENTEN is 90.5±19.9 minutes, whilst transosseous-equivalent full-thickness tendon repair without REGENETEN (i.e. standard of care) duration was 76.6±17.6 (p <0.0001); indicating an incremental procedure time of 13.9 minutes (Ruiz Ibán et al., 2023) . This is because REGENETEN is implanted in phase 4 of the surgical repair procedure in addition to implanting suture anchors (as surgical repair with sutures or anchors is required in addition to REGENETEN). If surgical repair was performed, this was immediately prior to applying REGENETEN (D. J. Bokor et al., 2015; Thon et al., 2019).

Table 5 Description of surgical procedures with use of REGENETEN in both populations

-	**Subpopulation 2**	**Incremental Procedure time**
Phase 1	Anaesthesia and skin penetration	-
Phase 2	Debridement, diagnosis and bursectomy	-
Phase 3	Standard arthroscopic or mini-open surgical repair (Sutures or anchors)[a]	-
Phase 4	**Arthroscopic surgical repair with REGENETEN**	**13.9 minutes(35)**

Source: Applicant feedback

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

Clinical management after the use of health technology

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, *after* the use of the proposed health technology:

Post-operative care

Following the procedure (performed arthroscopically or 'mini-open' approach), standard pain management measures should be undertaken. Specifically, post-operative care in Bokor et al. for patients with symptomatic FTRCTs, an 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).

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, after the use of the comparator health technology:

As provided in Figure 2, the post-operative rehabilitation algorithm for the comparator health technology includes either:

- improvement
- no improvement: requires further investigation or revision surgery

Note failure of rotator cuff repairs is reportedly on average 20-40% after primary rotator cuff repairs and is even higher in specific use cases including revision cases (37, 38). Re-tear of a rotator cuff repair has been associated with a multitude of factors including patient age, tear dimensions, and tendon tissue quality (40). 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. With over one-quarter of repairs failing to achieve durable integrity (i.e. re-tears) of the rotator cuff at two years (54), the inability to obtain high healing rates has spurred the investigation of biological options to augment rotator cuff repairs (22) (*e.g. application of REGENETEN in surgical repair of rotator cuff tears*).

Describe and explain any differences in the healthcare resources used *after* the proposed health technology vs. the comparator health technology:

Healthcare system perspective

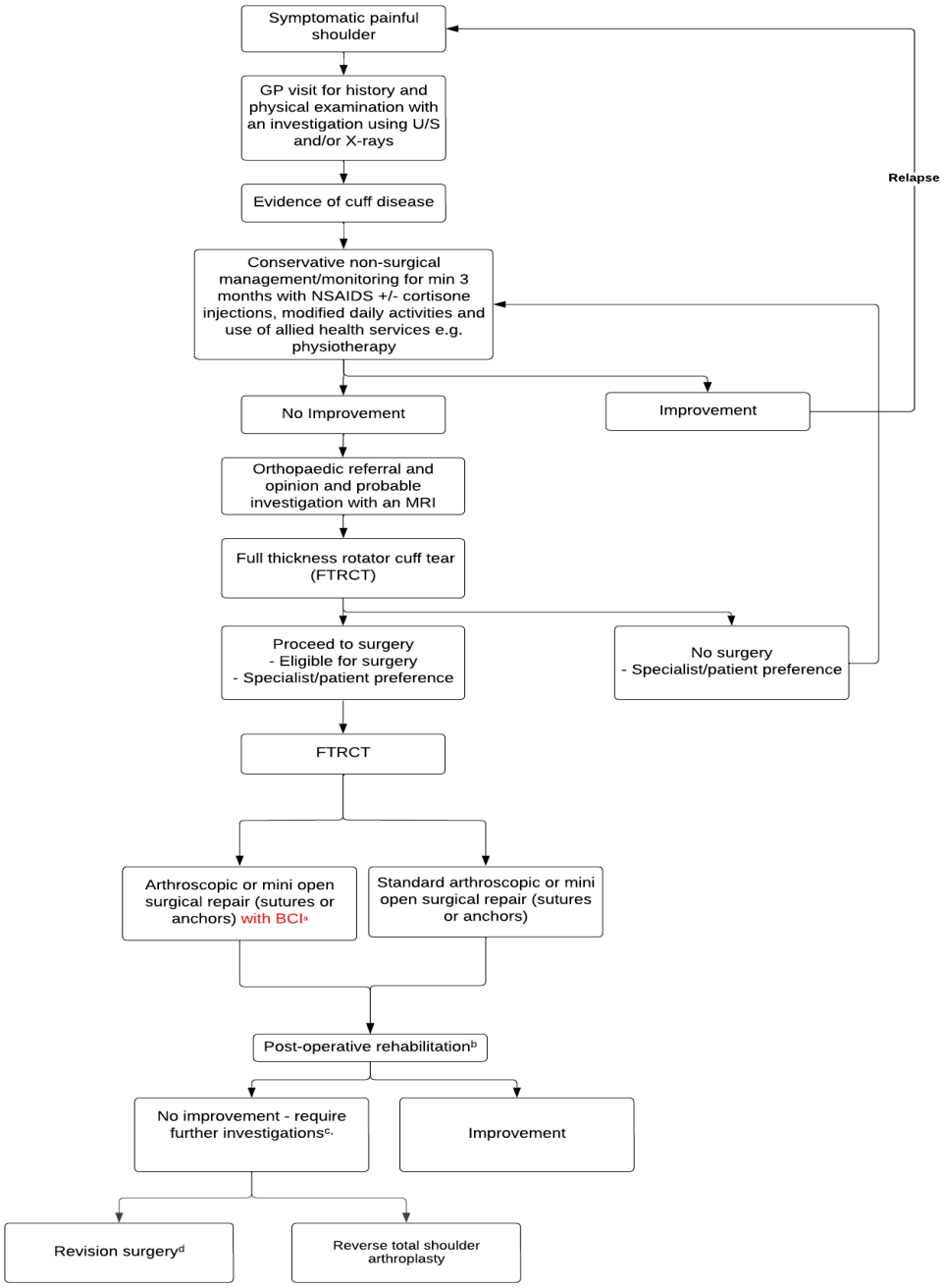
A potential decrease in hospital resources (operative) if the application of REGENETEN results in fewer patients requiring subsequent surgical revision, due to clinical failure (I.e. re-tear) of the primary rotator cuff tear procedure. Bokor et al. (1, 2) reported no tear progression or re-tears were observed during 24-month follow-up. However, in a population with advanced FTRCT disease (large and massive tears), two patients (9%) had clinical failure, with one requiring revision surgery with reverse shoulder arthroplasty, due to progression of patient's arthritis and further atrophy of rotator cuff (Thon et al 2019 (22)) (see efficacy results for REGENETEN in Table 6 – attached as appendix).

Insert diagrams demonstrating the clinical management algorithm with and without the proposed health technology:
Note: *Please ensure that the diagrams provided do not contain information under copyright.*

The Applicant's current and proposed clinical management algorithm was based on consultation with experts [Application Form, p11], as there are currently no Australian specific guidelines for

repair of rotator cuff tears. The place of REGENETEN, performed in addition to standard arthroscopic or mini-open surgical repair was highlighted in red during the preparation of the PICO confirmation. In addition, downstream options were also added during the preparation of the PICO confirmation. The current and proposed clinical management algorithm for identified population is provided in *Figure 2*.

Figure 2: - Current and proposed algorithm for FTCRT



Source: Compiled from [Application Form, p21

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

[a] All patients with FTRCTs in Bokor et al 2015 (1) and Thon et al. 2019 (22) received bovine BCI after surgical repair (sutures or anchors)

[b] Applicant stated that after receiving surgery patients are followed up for 3 months as routine practice [Application form, p15]

[c] Possible investigations could include imaging (MRI), physical therapy sessions, and treatments for pain management

[d] 2 patients with FTRCTs (large or massive) had clinical failure in Thon et al. 2019 (22), resulting in 1 requiring revision surgery with reverse shoulder arthroplasty, due to progression of arthritis

Summary of Evidence

Provide one or more recent (published) high quality clinical studies that support use of the proposed health service/technology. At 'Application Form lodgement',
Published RCT:

#	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication
1	Prospective, multi-centre, randomised, triple blinded (patient, outcome assessor, and data analyst-blinded) clinical trial of one year's duration.	NCT04444076 The effect on healing rate on the addition of bioinductive implant to a rotator cuff repair. Augmentation of a Transosseous-Equivalent Repair in Posterosuperior Nonacute Rotator Cuff Tears With a Bioinductive Collagen Implant Decreases the Retear Rate at 1 Year: A Randomized Controlled Trial	Comparative study of RCR with REGENETEN vs Standard RCR. 1-year results from this study (57 patients), show: • Significantly lower re-tear rates in REGENETEN group • No differences in post-operative complications between groups • failure rate at the musculotendinous junction significantly lower in REGENETEN group Post-operative fatty infiltration was lower in REGENETEN group Population: Non-acute symptomatic (>3 months) full-thickness posterosuperior cuff tear with anteroposterior size between 1 and 4 cm Intervention: Transosseous-equivalent full-thickness tendon repair with REGENETEN Comparator: Standard surgical repair: transosseous-equivalent full-thickness tendon repair without REGENETEN Outcomes: CMS; ASES Score; EQ-5D-5L; Brief Pain Inventory; MRI – integrity of repaired tendon using the sugaya score;	https://pubmed.ncbi.nlm.nih.gov/38158165/ https://clinicaltrials.gov/ct2/show/NCT04444076 Ruiz Iban (CSR). (2023). *Investigator Initiated Study Clinical Report: Final Results (Ruiz Iban)*. Smith & Nephew. Ruiz Ibán, M., et al. (2024). Augmentation of a Transosseous-Equivalent Repair in Posterosuperior Nonacute Rotator Cuff Tears With a Bioinductive Collagen Implant Decreases the Retear Rate at One Year: A Randomized Controlled Trial. *Arthroscopy*. https://doi.org/10.1016/j.arthro.2023.12.014 Ruiz Iban, et al. (2021). Footprint preparation with nanofractures in a supraspinatus repair cuts in half the retear rate at 1-year follow-up. A randomized controlled trial. *Knee Surg Sports Traumatol Arthrosc*, *29*(7), 2249-2256. https://doi.org/10.1007/s00167-020-06073-7 Manuscript of the 2 years data has been submitted, pending publication.	June 2024

#	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication
2	Prospective, blinded, single surgeon randomised controlled trial of two-year duration	Independent RCT by Dr Camacho-Chacon Biological repair vs mechanical repair of the rotator cuff in small and medium rotators: a prospective randomised trial	2-year follow-up results Population: Patients presenting with a small to medium size posterosuperior rotator cuff tear confirmed by MRI Intervention: Tendon repair with IBR Comparator: Standard Surgical Repair: transosseous equivalent repair without augmentation Outcomes: ASES Score; VAS; CMS; Biopsy; MRI; Satisfaction; Work Status; AEs	https://www.sciencedirect.com/science/article/abs/pii/S1058274624003239	September, 2024

Identify yet-to-be-published research that may have results available in the near future (that could be relevant to your application).

Do not attach full text articles; this is just a summary (repeat columns as required).

Yet to be published evidence:

#	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
3	Comparative, randomised controlled trial, multi-centre study, Level II	Clinical Trial on the Effect of REGENETEN Bioinductive Implant in the Supraspinatus Tendon Repair. (MALLAMANGUITO) NCT04444076 - The Effect on healing rate of the addition of a bioinductive implant to a rotator cuff repair.	Comparative study of RCR with REGENETEN vs Standard RCR. 2 yr result manuscript has been submitted, awaiting publication. Published 1-year results from this study (57 patients), show: • Significantly lower re-tear rates in REGENETEN group • No differences in post-operative complications between groups • failure rate at the musculotendinous junction significantly lower in REGENETEN group • Post-operative fatty infiltration was lower in REGENETEN group	Journal article not yet published. Manuscript has been submitted: AUGMENTATION WITH A BIOINDUCTIVE COLLAGEN IMPLANT OF A POSTEROSUPERIOR CUFF REPAIR IS SAFE AND EFFECTIVE. A BRIEF UPDATE OF THE RESULTS OF A RANDOMIZED CONTROLLED TRIAL https://clinicaltrials.gov/ct2/show/NCT04444076	Estimate: April 2025

Supplementary evidence:

#	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
4	Australian, Prospective, multi-centre randomised controlled trial of two-year duration.	Does Collagen Scaffold Augmentation of High-Grade Partial Rotator Cuff Tendon Tears Improve Early Functional Recovery Compared to Rotator Cuff Repair (PROCTOR)	The overall aim of this RCT is to assess the safety and efficacy of augmentation with the REGENTEN bioinductive scaffold/implant, versus the standard surgical rotator cuff repair procedure, for symptomatic partial thickness rotator cuff tears Population: High-grade (≥50%) partial thickness rotator cuff tear as noted on a 3-Tesla MRI scan Intervention: Isolated REGENETEN Comparator: Standard Surgical Repair: Arthroscopic decompression and double row rotator cuff repair Outcomes: ASES score, SANE, CMS, VR-12, MRI Evaluation (final results only), AEs	Wang (CSR Interim), A. (2023). *Investigator Initiated Study Clinical Report: Interim Results (ACTRN12620000926932)*. Smith & Nephew. Wang, A. (2021). *Does Collagen Scaffold Augmentation of High Grade Partial Rotator Cuff Tendon Tears Improve Early Functional Recovery? A Randomized Controlled Trial (Study Protocol)*. https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=380029	N/A
5	Non-randomised, single-arm, single- centre Level IV	Preliminary investigation of a biological augmentation of rotator cuff repairs using a collagen implant: a 2-year MRI follow-up (ACTRN12611001082998)	Repairs of full-thickness rotator cuff lesions in 9 patients were performed using collagen implant. Evaluated using MRI at 3,6, 12 and 24 months post-operatively. • Clinical scores improved significantly (p <.001) • Significant mean tendon thickness increased (p <.0001) • No re-tears observed during the 24-month follow-up	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4617212/	2015

#	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
6	Non-randomised, single-arm, retrospective study Level IV	Histologic Evaluation of Biopsy Specimens Obtained After Rotator Cuff Repair Augmented with a Highly Porous Collagen Implant	Biopsies of collagen implant/host-tissue constructs from 7 patients undergoing a second arthroscopic procedure after arthroscopic rotator cuff repair augmented with a collagen implant. • increased collagen formation, maturation, and organisation over the surface of the implant at 3 months • newly generated tissue at 6 months	https://www.ncbi.nlm.nih.gov/pubmed/27650821	2017
7	Observational registry study Level IV	Rotation Medical Bioinductive Implant Database Registry (REBUILD) Registry (NCT02784600)	Registry of 173 patients with partial (N=90) or full-thickness (N=83) rotator cuff lesions who underwent surgery using collagen implant. Post-operative assessments were performed at 2, 6, 12 weeks and 6 and 12 months. • Both groups experienced statistically significant (p<0.001) improvement in VAS, SANE, VR-12 PCS, ASES and WORC scores	https://clinicaltrials.gov/ct2/show/NCT02784600	2019
8	Non-randomised, single-arm, single-centre Level IV	Evaluation of Healing Rates and Safety With a Bioinductive Collagen Patch for Large and Massive Rotator Cuff Tears: 2-Year Safety and Clinical Outcomes	23 patients underwent repair of FT large/massive RCT augmentation with REGENTEN. MRI scan used to confirm tendon healing and thickness at minimum 6 months postoperatively, ultrasound used to assess thickness at 3-, 6-, 12-, 24- months. • 96% healing rate via US and MRI • 0 AEs attributed to REGENETEN	https://pubmed.ncbi.nlm.nih.gov/31150274/	2019

#	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
9	Non-randomised, single-arm, single-centre Level IV	Bioinductive collagen implants facilitate tendon regeneration in rotator cuff tears	30 patients (PTRCT & FTRCT) underwent arthroscopic repair and augmentation with REGENETEN. Preoperatively and at 6 and 12 months postoperatively, VAS, ASES, CMS were evaluated. • statistically significant improvements vs pre-operative values in VAS pain score (p=0.003), ASES (p=0.001) and CMS (p=0.001) at 6 months post-operatively, which were sustained at 1 year	https://jeo-esska.springeropen.com/articles/10.1186/s40634-022-00495-7	2022
10	Non-randomised, single-arm, multi-centre Level IV	Retear rates and clinical outcomes at 1year after repair of full-thickness rotator cuff tears augmented with a bioinductive collagen implant: a prospective multicenter study	115 patients with FTRCTs unresponsive to CMM with shoulder pain lasting >3 months underwent augmenting single- or double-row arthroscopic repair of FTRCTs with REGENETEN. • ASES and CMS scores significantly improved between the baseline and 1 year	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7910780/	2021
11	Non-randomised, single-arm, multi-centre Level IV	Two-year outcomes with a bioinductive collagen implant used in augmentation of arthroscopic repair of full-thickness rotator cuff tears: final results of a prospective multicenter study.	115 patients underwent augmenting single- or double-row arthroscopic repair of FTRCTs with REGENETEN. • 97.1% surveyed were satisfied with the procedure; 100% of patients surveyed would recommend the procedure to a friend • >90% of patients had significant post-operative improvements in ASES Shoulder and CMS scores that exceeded respective MCIDs (p<0.001)	https://www.sciencedirect.com/science/article/abs/pii/S105827462200547X?via%3Dihub	2022

#	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
12	Non-randomised, single-arm, single-centre Level IV	Bio-inductive implant for rotator cuff repair: our experience and technical notes.	4 patients with RCTs (1x PTRCT, 3x FTRCT) underwent surgical repair with REGENETEN. • no complications were found at 6 weeks follow-up • Increase in procedure duration by 10 minutes	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7944686/	2020
13	Economic analysis	Resorbable Bioinductive Collagen Implant Is Cost Effective in the Treatment of Rotator Cuff Tears	Decision analytic model to compare expected incremental cost and clinical consequences for a cohort of patients with FTRCT. • REGENETEN + conventional RCR results in incremental costs of $232,468 and an additional 18 healed RCTs/100 treated patients over 1 year. • Estimated ICER = $13,061/healed RCT compared to conventional RCR alone	https://www.sciencedirect.com/science/article/pii/S2666061X23000020#:~:text=Results,treated%20patients%20over%201%20year.	2023
14	Retrospective Case Series, registry, multi-centre Level IV	Patient-Reported Outcomes After Use of a Bioabsorbable Collagen Implant to Treat Partial and Full-Thickness Rotator Cuff Tears	1 year FU of 173 patients (PTRCT and FTRCT) to assess PROMs at 2, 6, and 12weeks, 6months and 1 year. • FTRCT: ○ MCIDs achieved in VAS pain from 2 weeks and ASES score from 3 months	https://www.sciencedirect.com/science/article/abs/pii/S0749806319301562?via%3Dihub	2019
15	Retrospective Case Series, registry, multi-centre Level IV	Full-Thickness Rotator Cuff Tears Can Be Safely Treated With a Resorbable Bioinductive Bovine Collagen Implant: One-Year Results of a Prospective, Multicenter Registry	1 year FU of 192 FTRCT patients augmented with REGENETEN. • At 6 months and 1 year, ASES, SANE, VR-12 PCS and WORC were significantly improved • Mean duration of post-operative recovery (days): sling time, 36.3; return to driving, 24.0; return to work, 48.4; return to non-overhead sports, 105.4, return to overhead sports, 131.7	https://www.arthroscopysportsmedicineandrehabilitation.org/article/S2666-061X(21)00119-X/fulltext	2021

#	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
16	Literature review of case studies and registry data, multi-centre, Level V	Regeneten bio-inductive collagen scaffold for rotator cuff tears: indications, technique, clinical outcomes, and review of current literature.	• 89–91% patient satisfaction FTRCT (2 studies) • 96–100% healing rate FTRCT (2 studies) • 3.9% reoperation rate (10/251; 5 studies) • 5.9% failure rate (5 studies) • 9.9% complication rate (5 studies)	https://aoj.amegroups.com/article/view/5816/html#B17	2020
17	Comparative, randomised controlled trial, multi-centre study, Level II	Use of bio inductive bovine collagen patch augmentation for full thickness cuff tears - 12-month follow up results of an ongoing prospective randomised trial.	Comparative study of RCR with REGENETEN vs Standard RCR. 1-year results from this study (56 patients), show: • lower re-tear rates in REGENETEN group • Improved function and pain scores in REGENETEN group (CMS and VAS pain) • 3 cases of shoulder stiffness/adhesive capsulitis (2 REGENETEN group, 1 control group)	Interim results presented at The European Society for Surgery of the Shoulder and Elbow (SECEC) Annual Congress; September 7–9, 2022; Dublin, Ireland.	

* Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.

**Provide high level information including population numbers and whether patients are being recruited or in post-recruitment, including providing the trial registration number to allow for tracking purposes. For yet to be published research, provide high level information including population numbers and whether patients are being recruited or in post-recruitment.

*** If the publication is a follow-up to an initial publication, please advise. For yet to be published research, include the date of when results will be made available (to the best of your knowledge).

PTRCTs. Partial Thickness Rotator Cuff Tears; RCTs, Rotator Cuff Tears; RCR, Rotator Cuff Repair; ICER, incremental cost-effectiveness ratio; FU, follow up; MCIDs, minimal clinically important differences; VAS, visual analogue scale; ASES, American Shoulder and Elbow Surgeons

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Appendix

Table 3 Description of patient populations for REGENETEN in rotator cuff surgical repair

Study ID	Indication	N	Study type	Selected patient criteria	Country
PEER REVIEW					
	FTRCT only				
Thon et al. 2019	• Large (2-tendon): 11 (48%) • Massive (3-tendon): 12 (52%) • Revision surgery 16 (70%)	23	Prospective, OL, NR, single arm, MC. Level IV[a]	• Patients aged ≥ 30 years • Large or massive rotator cuff tear > 3cm and retraction of at least 3cm measured on preoperative MRI • Exclusion criteria: Patients aged < 30 years; extensive prior treatment incl. physical therapy, injections AND/OR anti-inflammatory medication for >6 weeks before surgery; Hamda grade ≥ 3 preoperative rotator cuff arthropathy; Goutallier grade ≥ 3 muscle atrophy, <2-year clinical follow-up and unwilling to complete study protocol	US
Bushnell BD, et al. 2021a Bushnell BD, et al. 2022	• Medium (1-3cm): 66 (57.4%) • Large (3-5cm): 49 (42.6%)	115	Prospective, OL, NR, single arm, MC. Level IV[a]	• Patients aged ≥ 21 yearsmedium (1-3 cm) or large (3-5 cm)101 FTRCTs often including the supraspinatus tendon planned for surgical repair • Chronic shoulder pain lasting longer than 3 months that was unresponsive to conservative therapy including – but not limited to – pain medication, physical therapy, and injections	US
McIntyre LF, et al. 2021	• Small (<1cm): 12 (5.7%) • Medium (1-3cm): 92 (43.8%) • Large (3-5cm): 75 (35.7%) • Massive (>5cm): 31 (14.8%)	192	Prospective, OL, NR, single arm, MC. Level IV[a]	• Patients aged ≥ 21 years[e] (understands English) • Willingness to participate	US
Iban, 2022 NCT04444076	• Medium (1-3cm) • Large (3-5cm)	124	Comparative, RCT, MC, Level II[a]	• Supraspinatus Full Thickness Tear (+/- infraspinatus) • <3cm retraction of supraspinatus tendon • <4cm AP extension (size of rupture) • Tear was fully reparable • >18 years	Spain
	mixed FTRCT and PTRCT				
ACTRN12611001082998 Bokor et al. (2015)	FTRCT: 8 (89%) • Medium (1-3cm) PTRCT: 1 (11%) • High grade (10mm), bursal sided.(converted to FTRCT at surgery) All supraspinatus tendon.	9	Prospective, OL, NR, single arm, SC. Level IV[a]	• Patients aged 40-66 years at surgery • Chronic shoulder pain > 3 months (resistant to analgesics, anti-inflammatory medication, and physical therapy) Exclusion criteria: patients with shoulder instability; grade 3 ≥ chondromalacia; or grade 2 ≥ fatty infiltration of supraspinatus. Recent steroid use, insulin-dependent diabetes, heavy smoking, genetic collagen disease, chronic inflammatory disease, and index shoulder with previous cuff surgery. Contraindications: hypersensitivity to collagen	Australia

Study ID	Indication	N	Study type	Selected patient criteria	Country
Camacho-Chacon JA, et al. 2022	Supraspinatus tendon FTRCT: 12 • 1 small • 7 large • 4 massive PTRCT: 18 • 11 High • 7 medium	30	Prospective, OL, NR, single arm, SC. Level IV[a]	• Patients >18 years • Diagnosis of partial or total rupture of the rotator cuff with failure of conservative treatment (analgesics, anti-inflammatory medication, and physical therapy) after 6 months • absence of previous surgeries • consent for surgical intervention and specific for surgery and the performance of percutaneous biopsy 6 months after surgery • absence of infectious complications after arthroscopy	Spain
McIntyre L, et al. 2019 NCT02784600	PTRCT: 90 (52%) • Grade 1 (<3mm): 15 (16.7%) • Grade 2 (3-6mm): 34 (37.8%) • Grade 3 (>6mm): 41 (45.5%) FTRCT: 83 (48%) • Small (<1cm): 4 (4.8%) • Medium (1-3 cm): 42 (50.6%) • Large (3-5 cm): 25 (30.1%) • Massive (>5 cm) 12 (14.5%)	173	Observational registry study, MC. Level IV[a]	• Patients aged ≥ 21 years (understand English) • Exclusion criteria: hypersensitive to bovine-derived materials	US
Thon SG, et al. 2020 19	PTRCT: 136 FTRCT: 115	251	SLR of case study data Level IV[a]	• As per included publications: ○ Bokor et al 2015 (1) ○ Bokor et al 2016 (2) ○ Shlegel et al 2018 (33) ○ Thon et al 2019 (22) ○ McIntyre et al 2019 (43)	US
FTRCT only					
Camacho-Chacon et al. 2022	FTRCT Small <1cm) and medium (1-3cm)	*60*	RCT,MC, , Level II[a]	• Supraspinatus full thickness tear, tear pattern did not exceed dimensions of the REGENETEN implant (20x26mm). Patients had intact rotator cable. • Exclusion: Rheumatologic disease, active steroid use, previous ipsilateral rotator cuff surgery, significant subscapularis tear, post-traumatic tears, tear pattern requiring significant side-to-side tendon repair, large u-	Spain

Study ID	Indication	N	Study type	Selected patient criteria	Country
				shaped tears, intra-articular pathology such as SLAP, bankart or chondral lesions.	
Ferreira Barros A, et al. 2022	FTRCT Medium (1-3cm) Large (3-5cm)	*120*	RCT,MC Level II[a]	• Supraspinatus full thickness tear, Bateman grade 2-3 (~Cofield medium-large) • Exclusion: Infraspinatus and/or subscapularis tears	Portugal
	mixed FTRCT and PTRCT				
REBUILD Registry NCT02784600 *Completion: Dec 2019* (Results in McIntyre L, et al. 2019, Bushnell 2021b	PTRCT or FTRCT	*483*[c]	Observational registry study, MC. Level IV[a]	• Patients aged ≥ 21 years (understand English) • Exclusion criteria: hypersensitive to bovine-derived materials	US
Post-market evaluation NCT02200939	PTRCT or FTRCT supraspinatus	*148*	Prospective, OL, NR, parallel assignment, MC. Level IV[a]	• Patients aged ≥ 21 years (understand English) • Medium or large PTRCT OR very small FTCRT • Chronic shoulder pain > 3 months unresponsive to conservative therapy (pain medication, physical therapy and injections) • MRI of shoulder within 60 days • Willing to comply with post-operative rehabilitation • Exclusion criteria: massive rotator cuff tears (≥5cm), acute rotator cuff tears, previous rotator cuff surgery, patients with shoulder instability; grade 3 ≥ chondromalacia; or grade 2 ≥ fatty infiltration of supraspinatus. Recent steroid use, insulin-dependent diabetes, heavy smoking, genetic collagen disease, history of autoimmune disorders, chronic inflammatory disease, and index shoulder with previous cuff surgery. Contraindications: hypersensitivity to bovine-derived materials	US
Amplitude Registry (Global incl. Australian patients)[f]	PTRCT or FTRCT	*TBD*	Registry Level IV[a]		UK Hong Kong Additional cites to come: Australia (April 2023) Germany France Spain Portugal
Australia retrospective return to work	PTRCT or FTRCT	*TBD*	Retrospective cost benefit analysis	• Patients >18 • Failure of conservative medical management • Presenting with PTRCT or FTRCT	Australia

Study ID	Indication	N	Study type	Selected patient criteria	Country
comparative Cost Benefit Analysis[f]			Level IV[a]		

Source: Compiled from Application Form and accessing Clinicaltrials.gov + amended as per 'Summary of Evidence' attachment for resubmitted application

Abbreviations: FTRCT = full-thickness rotator cuff tear; MC = multi-centre; NR = non randomised; OA = osteoarthritis; OL = open label; PTRCT = partial-thickness rotator cuff tear; Retro = retrospective; RA = rheumatoid arthritis; SC = single-centre; US = United States; int = intermediate; RCT = randomised controlled trial; UK = United Kingdom

[a] National Health and Medical Research Council (NHMRC) levels of evidence

[b] Includes comparator arm with surgical treatment of partial-thickness rotator cuff tears using standard techniques

[c] Listed as enrolled on Clinicaltrials.gov; Application stated Registry of 173 patients, with PTRCT (n=90) and FTCRT (n=83)

[d] limited inclusion criteria proposed to better reflect patients encountered in real-world clinical practice

[e] limited inclusion criteria proposed to better capture the wide breadth of patient and full-thickness tear causes encountered by clinicians

[f] public references and internal report not yet available, accumulation of data by S+N is ongoing and will be included in resubmitted ADAR.

Table 6 Summary of current clinical evidence for surgical repair with REGENETEN (REGENETEN)

Study ID	N	Study type	Key outcomes results	Country
PEER REVIEW				
		FTRCT only		
Thon et al. 2019	23	Prospective, OL, NR, single arm, MC Level IV[a]	• No adverse events attributed to implant • Clinical failure[c] = 2 patients (9%), 1 requiring additional surgery arthroplasty, due to progression of pain and dysfunction • MRI rotator cuff thickness = 5.13 ±1.06mm • Mean ASES at final follow-up = 82.87 ±16.68	US
Bushnell BD, et al. 2021a	115	Prospective, OL, NR, single arm, MC. Level IV[a]	• . At 1 year, the minimally clinically important difference for ASES and CMS was met by 91.7% (95% CI: 84.9-96.1) and 86.4% (95% CI: 78.2-92.4) of patients, respectively • Of 9 reported reoperations in the operative shoulder, only 2 were considered potentially related to the collagen implant. • 13 retears (11.3%) at 3 months and 19 (16.5%) at 1 year • At 1 year, no visible boundary between the collagen scaffold/new tissue was not observed or could not be determined in all available (100%). • At 1 year, 110 of 114 patients (96.5%) reported that they "agreed/ strongly agreed" that they were satisfied with surgery and 4 (3.5%) that they "disagreed/strongly disagreed." • mean sling time of 38.7 days (SD, 18.3) • mean of 22 days (SD, 12.45) spent in physical therapy • mean time to return to work was 44.1 days (SD, 64.8) and to return to normal activities was 124.6 days (SD, 60.6)	US
Bushnell BD, et al. 2022			• Between baseline and 2-year follow-up, mean total thickness of the supraspinatus tendon increased by 12.5% for medium tears and by 17.1% for large tears. • Radiographic re-tear was noted in 7/61 available • patients (11.5%) with medium tears, and in 14/40 patients (35.0%) with large tears. • MCID was achieved by >90% of patients with both medium and large tears for both ASES and CMS • 2 serious adverse events classified by the treating surgeon as being possibly related to the device and/or procedure (1 case of swelling/drainage and 1 case of intermittent pain).	

Study ID	N	Study type	Key outcomes results	Country
McIntyre LF, et al. 2021	192	Prospective, OL, NR, single arm, MC. Level IV[a]	• Statistically significant improvement in outcomes for the SANE, VR-12 PCS, ASES and WORC over 1 year of registry follow-up • MCID achieved at 1 year for SANE in 84.3% patients (161/191), for VR-12 MCS in 40.3% (77/191), for VR-12 PCS in 78.5% (150/191), for ASES in 90.5% (86/95), and for WORC in 87.2% (116/133). • Average time in a sling for 188 patients was 36.3 days (SD, 16.8) • Return to driving occurred after an average of 24.0 days (SD, 25.8) in 135 patients and work after 48.4 days (SD, 52.1) in 128 patients • Return to nonoverhead athletics averaged 105.4 days (SD, 77.2) in 71 patients and overhead athletics 131.7 days (SD, 77.3) in 42 patients • Total number of physical therapy visits among 144 patients averaged 21.8 (SD, 16.2). • Twenty patients (10.4%) experienced serious complications, including 18 (9.4%) who underwent revision surgeries	US
Ruiz Iban, 2022 NCT04444076	57	Comparative, RCT, MC, Level II[a]	• Interim results: • tendon retears (Sugaya >3) were present in 25% of control patients and 3.5% of REGENETEN patients • the tendon thickness in non-retear patients was not yet significantly different between groups in this interim report • 79% of REGENETEN patients had a Sugaya Classification ≤II compared to 46% of patients without REGENETEN. • There were no additional post-operative complications in the REGENETEN group compared to the control group.	Spain
Barros	56	Comparative RCT, Level II [a]	• Interim results: • REGENETEN group: Constant Score average was 49 pre-op, at 3 months was 70, at 6 months was 86, and at 12 months was 89. • Control group: Constant score average was 52 pre-op, 62 at 3 months, 78 at 6 months and 82 at 12 months. • REGENETEN VAS pain average was 7.5 pre-op, 2.9 at 3 months, 1.5 at 6 months, 0.7 at 12 months. • Control VAS pain average was 7.2 pre-op, 4.5 at 3 months, 2.1 at 6 months, 1 at 12 months. • In the REGENETEN group there were 2 re-ruptures (7%) and 2 adhesive capsulitis. In the Control group there were 4 re-ruptures (13%) and 1 adhesive capsulitis.	
		mixed FTRCT and PTRCT		
ACTRN12611001082998 Bokor et al. (2015)	9	Prospective, OL, NR, single arm, SC Level IV[a]	• Significantly improved clinical scores (Constant-Murley and ASES; p<0.01) • Significant mean tendon thickness increased (p<0.01) • No re-tears observed during 24-month follow-up	Australia
Arnoczky 2017	7	Retro, OL, NR, single arm, SC Level IV[a]	Biopsy related outcomes: • Increased collagen formation, maturation and organisation • Newly generated tissue at 6 month[b]	US
Camacho-Chacon JA, et al. 2022	30	Prospective, OL, NR, single arm, SC. Level IV[a]	• VAS score improved significantly (P = 0.003), from 7.23 ± 0.77 at the beginning to 0.57 ± 1.13 at six months and 0.27 ± 0.94 at one year	Spain

Study ID	N	Study type	Key outcomes results	Country
			• ASES and Constant scores also improved significantly from 48.03 ± 1.18 to 85.93 ± 7.25 at six months and 87.80 ± 7.00 at one year (P = 0.001) and from 58.60 ± 1.61 to 85.37 ± 6.51 at six months and 90.23 ± 5.88 at one year (P = 0.001), respectively. • FTRCT: At six months after surgery, there was a significant increase (P = 0.001) in the induction of new tissue of the rotator cuff, going from a mean preoperative thickness in partial tears of 4.18 ± 0.29 mm to 6.02 ± 0.29 mm with an average increase in tendon thickness of 1.84 ± 0.29 mm. • 0 re-ruptures	
Micheloni GM, et al. 2020	4	Prospective, OL, NR, single arm, SC. Level IV[a]	• No complications occurred at 6 months follow-up	Italy
McIntyre L, et al. 2019 NCT02784600	173	Observational registry study, MC. Level IV[a]	PTRCT: • statistically significant improvement in outcomes for VAS, SANE, VR12 physical component,ASES, and WORC over 12 months of study follow-up (P < .05). • average time in a sling was 10.6 days for those without biceps surgery and 27.7 days for patients who underwent concomitant tenodesis • Patients returned to driving in an average of 14.6 days, and to work, in 37.3 days (9.4 days for sedentary jobs and 72.9 for physical jobs). • Return to athletics averaged 65.6 days, with return to overhead athletics at 117.9 days. • Patients used opioid medicines for pain control for an average of 18.3 days. • The total number of PT visits averaged 20.6	US
Thon SG, et al. 2020	251	SLR of case study data Level IV[a]	• As per included publications: o Bokor et al 2015 o Bokor et al 2016 o Shlegel et al 2018 o Thon et al 2019 o McIntyre et al 2019	US

Source: pp6-7 of Application Form and Thon et al. 2019 – New publications added

Abbreviations: ASES = American Shoulder and Elbow Surgeons; FTRCT = full-thickness rotator cuff tear; MC = multi-centre; MRI = magnetic resonance imaging; NR = non randomised; OL = open label; PTRCT = partial-thickness rotator cuff tear; Retro = retrospective; RA = rheumatoid arthritis; SC = single-centre; US = United States; int = intermediate; med = medium; SANE = Single Assessment Numeric Value VR-12 = Veterans RAND 12 Item Health Survey; WORC = Western Ontario Rotator Cuff Index; VAS = visual analogue scale; SLR = Systematic literature review; MCID = Minimal clinically important difference; MCS = Mental Component Score; PCS; Physical Component Score

[a] National Health and Medical Research Council (NHMRC) levels of evidence

[b] Implant generated host tissue rapidly matured into tendon tissue

[c] Was defined as lack of healing on either imaging modality (US 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.