Australian Government

Department of Health

RATIFIED
PICO CONFIRMATION

Application 1569:

Chitosan-based cartilage biomatrix implant (BST-CarGel), in conjunction with the marrow stimulation technique (microfracture), for repair of focal cartilage defects (PLAC co-dependent)

Table of abbreviations

ACI	Autologous chondrocyte implantation
CBI	Chitosan-based cartilage biomatrix implant
CEA	Cost-effectiveness analysis
CT	Computed tomography
CTA	Computed tomography angiogram
CUA	Cost utility analysis
HRQoL	Health-related quality of life
ICRS	International Cartilage Repair Society
MACI	Matrix-induced autologous chondrocyte implantation
MBS	Medicare Benefits Scheme
MF	Microfracture
MRI	Magnetic resonance imaging
MSAC	Medical Services Advisory Committee
OA	Osteoarthritis
OAT	Osteochondral autograft transfer
PASC	PICO Advisory Sub-Committee
PICO	Patient-intervention-comparator-outcome
PLAC	Prostheses List Advisory Committee
PPICO	Patient-Prior tests-intervention-comparator-outcome
QALY	Quality adjusted life year
RCT	Randomised controlled trial
SOCAG	Specialist Orthopaedic Clinical Advisory Group
TJR	Total joint replacement
TKR	Total knee replacement
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

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

Component	Description
Patients	**Population 1:** Patients with radiologically confirmed International Cartilage Repair Society (ICRS) Grade 3 or 4 articular cartilage defect < 2 cm^2, with moderate knee pain. **Population 2:** Patients with radiologically confirmed International Cartilage Repair Society (ICRS) Grade 3 or 4 articular cartilage defect ≥ 2 cm^2, with an intact subchondral endplate and with moderate knee pain. Patients in Populations 1 or 2 who are ineligible for treatment include those who: 1. have evidence of advanced osteoarthritis in the joint of interest, or have generalised osteoarthritis; OR 2. have an inflammatory arthropathy; for example, rheumatoid arthritis or psoriatic arthritis; OR 3. have significant articular instability in the joint in question; for example, a ligament injury (patients who have had repairs to articular instability are not excluded).
Prior tests (for investigative medical services only)	Not applicable
Intervention	Chitosan-based cartilage biomatrix implant, in conjunction with microfracture (CBI+MF) (also known as augmented microfracture). The intervention is restricted to lesions in the knee, and may be used once per lesion (not once per patient).
Comparator	Population 1: Microfracture alone, in conjunction with standard of care Population 2: Microfracture alone, in conjunction with standard of care *While comparators for this application (1569) and similar current application 1578 should be as consistent as possible, there are slight comparator differences for larger lesions (population 2) between the two similar applications. (Please note: Population 2 in application 1569 is called Sub-Population 2 in application 1578)* *While mosaicplasty and alternative scaffold products available in Australia (e.g. JointRep™ and Chondro-Gide®, used in conjunction with microfracture) were initially proposed as comparators for application 1569, PASC confirmed they are not comparators for the product in this application [1569], but are for*

Component	Description
	Population 2/Sub-Population 2 in similar current application 1578. MACI and ACI are not comparators for either application. *However, the assessment reports for application 1569 (and similar current application 1578) should clearly detail the evidence (or lack thereof) for these interventions (including MACI/ACI), as well as newer interventions, against the product in application 1569 (and similar product in application 1578).* *This is for completeness, and to ensure robust information is available if MSAC wants to consider it.*
Outcomes	<u>Clinical effectiveness:</u> • Quality, quantity and structure of cartilage (quantity hyaline characteristic cartilage; proportion of lesion fill); • OMERACT (Outcome Measures in Rheumatology); • Time to weight bearing; • Symptoms and function; • Quality of life and patient satisfaction; and • Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score, Tegner Activity Scale, International Cartilage Repair Society (ICRS) Score, and Lysholm Knee Scoring Scale. <u>Safety</u>: Adverse events and serious adverse events related to treatment; Treatment failure (defined as percentage lesion fill < 70%) <u>Cost-effectiveness:</u> Resource use: surgical costs (surgical time, surgeon consult, including for total joint replacement/subsequent procedures), days as an inpatient, inpatient paramedical consults (e.g. physiotherapy), medical devices (e.g. knee brace), laboratory tests, diagnostic tests (including MRI, X-ray, computed tomography (CT), CT angiography (CTA), follow-up physiotherapy rehabilitation, medication for pain management, indirect costs (time to return to work, work days lost, health related quality of life), quality-adjusted life years (QALY). Data limitations may inhibit consideration of longer-term outcomes, such as time to return to work, and total joint replacement/subsequent procedures. Data permitting, longer term outcomes should be considered.

PICO or PPICO rationale for therapeutic and investigative medical services only

Research Question for assessment phase

What is the safety, effectiveness and cost-effectiveness of a chitosan-based cartilage biomatrix implant (in conjunction with microfracture), in patients aged 15-55 years with radiologically confirmed grade 3 or worse articular cartilage damage, with (smaller) lesions < 2 cm^2 or (larger) lesions ≥ 2 cm^2, where there is an intact subchondral endplate and moderate knee pain, compared to microfracture alone?

Population

PASC noted the two PICO populations are defined by trial data, which relate to 15–55 year-olds. However, PASC advised there is no reason to impose an upper age limit of 55, given many people in their 60s and 70s are active and would benefit from this procedure. PASC acknowledged MSAC may choose to have an age limit in the MBS item descriptor.

PASC advised that the PICO populations should explicitly state patients must be symptomatic, and should align with requirements in the existing MBS items, as well as reflecting the ARTG listing.

PASC noted the 2 cm^2 size references in the literature. However, PASC advised that, while the view that size is important is widely held (by clinical experts), there is no clear evidence that size is important, and no standard/accepted clinical practice guidelines.

After the PASC meeting, PASC clarified that lesion sizes for Populations 1 and 2 in this application (1569) and similar current application 1578 should be consistent, being:

- Population 1 = $\leq$ 2 cm^2
- Population 2 = > 2 cm^2

PASC noted that, for larger lesions (> 2 cm^2 = Population 2), it should be clear that the subchondral end-plate needs to be intact for the BST CarGel implant. If it is not intact, a joint replacement is indicated.

PASC noted that “articular cartilage defect” refers to discrete cartilage destruction, not general deterioration associated with rheumatoid arthritis. PASC also noted that it is acceptable to treat two adjacent areas, in close proximity.

PASC advised that, while inclusion criteria for the Stanish trial had an upper body mass index (BMI) limit of 30 kg/m^2, ARTG listing criteria would be sufficient. While a BMI limit is unlikely to be needed, PASC noted this BMI was different to that referenced in similar (but different product) application 1578 (BMI reference of 40 kg/m^2).

PASC queried if earlier MSAC application 1140 (Matrix-induced Autologous Chondrocyte Implantation [MACI] and Autologous Chondrocyte Implantation [ACI]) was relevant to application 1569 (and similar current application 1578). MSAC considered MACI and ACI in 2011 (as alternatives to mosaicplasty and microfracture), but did not support public funding for these interventions.

After the PASC meeting, the Department advised that, while MACI and ACI are not comparators for the product in application 1569 (or the product in similar application 1578), the assessment reports

for application 1569 (and similar application 1578) should clearly detail the evidence (or lack thereof) for these newer interventions against MACI/ACI. This is for completeness, and to ensure robust information is available if MSAC wants to consider it.

PASC noted that, while the knee is the most common site for this procedure, it is used in other parts of the body. However, PASC recommended the PICO and subsequent health technology assessment be restricted to the knee, given most evidence relates to this site.

Patients	**Population 1:** Patients with radiologically confirmed confirm Grade 3 or 4 articular cartilage defect $\leq$ 2 cm^2 with moderate knee pain. **Population 2:** Patients with radiologically confirmed confirm Grade 3 or 4 articular cartilage defect > 2 cm^2 with an intact subchondral endplate and with moderate knee pain. Patients in Population 1 or Population 2 are ineligible for treatment include those who[b]: 1. have evidence of advanced osteoarthritis in the joint of interest, or have generalised osteoarthritis; OR 2. have an inflammatory arthropathy, for example, rheumatoid arthritis, psoriatic arthritis; OR 3. have significant articular instability in the joint in question, for example a ligament injury (patients who have had repairs to articular instability are not excluded).

Symptoms of articular cartilage injuries are predominant in weight-bearing joints, such as the knee, hip and ankle [3]. Typically, patients with focal articular cartilage lesions present to their general practitioner with pain, swelling, mechanical symptoms, athletic and functional disability, and eventually osteoarthritis [4]. However, there are no pathognomonic symptoms for cartilage defects, and it is not uncommon that these types of lesions coexist with other lesions of abnormalities such as meniscal or ligamental lesions of the joint. As such, imaging is imperative for diagnosis [5] and physicians cannot rely on history and physical assessment alone.

Patients with ongoing symptoms, despite conservative management should undergo diagnostic imaging. In Australia, radiological evidence is usually provided by MRI, however, computed tomography arthrograms (i.e. where contrast is injected into the affected joint by the radiologist under CT imaging guidance) or other investigations are sometimes used. Specifically, accurate characterisation of the cartilage should be performed using MRI: to assess the lesion itself, but also the opposing cartilage and menisci [4]. In patients who are contraindicated to MRI, a computed tomography arthrogram will be performed. If the lesion involves subchondral bone, or if MRI is contraindicated, CT scanning may also be required [4]. An important part of the clinical workup is to distinguish focal lesions of the articular surface from degeneration of cartilage occurring as a

consequence of osteoarthritis [4].Plain x-ray and ultrasound cannot show cartilage damage and are not used in diagnosis.

Cartilage defects are graded according to the ICRS grading system (see Figure 1, and Table 6 in Appendix). Grade 3 defects are considered severely abnormal, with cartilage defects extending down more than 50% of the cartilage depth, as well as down to calcified layer; down to but not through the subchondral bone; or are blisters (see Figure 1). Grade 4 are severely abnormal, extending through the subchondral bone (Figure 1).

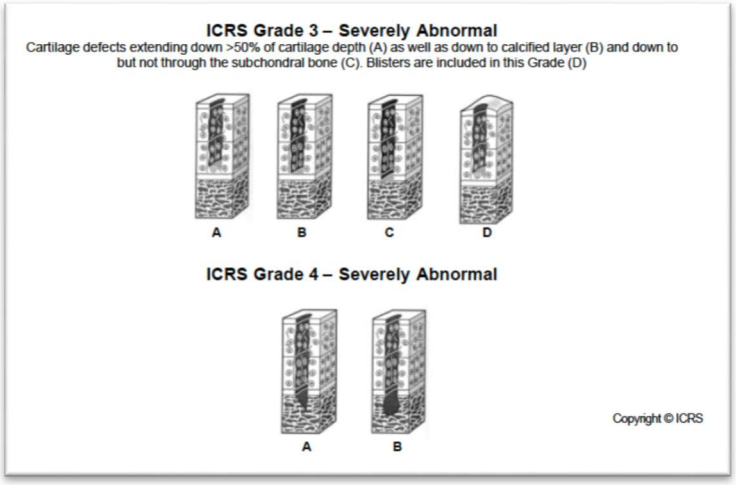

Figure 1 ICRS classification of cartilage injury
Source: ICRS Cartilage Injury Evaluation system. 2000.

Full thickness articular cartilage defects (Grade 3 or 4) have a poor capacity to heal due to the cartilage's isolation from systemic regulation, its lack of vessels and nerve supply [4]. If left untreated cartilage injuries can become degenerative and lead to premature early arthritis and affect the activities of daily living [6, 7]. Although rarely fatal, articular cartilage lesions severely reduce quality of life, ability to perform daily activities and imposes major economic burdens on individuals and society [8].

No Australian clinical guidelines exist for the management of articular cartilage lesions. The assessment report for the MSAC application 1140 of autologous chondrocyte implantation (ACI) / matrix-induced autologous chondrocyte implantation (MACI) (December 2010) provides a clinical decision-making pathway for the management of cartilage lesions of the knee based on expert clinical advice (MSAC Application Assessment Report Figure 1 pg 7[1]). The current and proposed clinical treatment algorithms were based on this report, along with expert advice. Current treatment is determined by the aetiology and size of the lesion, and the patient's comorbidities [4]. It is important to differentiate articular cartilage lesion effects from other pathologies that may be contributing to symptoms [4]. In particular, mechanical symptoms such as ligamentous injury or malalignment of the joint will require correction prior to considering cartilage repair [4].

Surgery is typically indicated for patients presenting with symptoms consistent with a full thickness cartilage defect (Grade 3 or 4) and mechanical symptoms despite an adequate trial of nonoperative

1 www.msac.gov.au/internet/msac/publishing.nsf/Content/E72BFBEC5447F91FCA25801000123B6D/$File/1140_Report_Final040211.pdf (accessed 31 October 2018)

management. The orthopaedic surgeon will determine treatment strategies for cartilage repair primarily based on the location and the size of the defect, with age and hence level of expected activity as important secondary considerations [5]. Treatment is complicated in patients with comorbidities such as ligamentous instability, deficient menisci or malalignment of the mechanical limb axis or extensor mechanism [4].

Patients with advanced osteoarthritis are generally not suitable for cartilage repair.

Prevalence of articular cartilage lesions

Articular cartilage lesions of the knee are relatively common, with an estimated prevalence of 60% found in patients undergoing knee arthroscopy [9-11]. Lesions in the hip and ankle are less common, full thickness acetabular lesions are seen in around 10% of hips treated for femoroacetabular impingement (FAI) [3]. Cartilage lesions of the ankle are often non-symptomatic, as such the prevalence is unclear [12]. A retrospective analysis of medical records from patients undergoing arthroscopy of the knee or ankle found that high grade (ICRS Grade 3 and 4) cartilage defects were significantly more prevalent in the knee (49.47%) compared to the ankle (26.31%) [12].

The prevalence of grade 3-4 lesions varies; localised full thickness cartilage lesions (grade 3-4) were found in 11% of patients undergoing knee arthroscopy [9]. APTA (2018) report that grade 3-4 lesions make up 30% to 60% of all articular cartilage lesions [13]. With a growing percentage of the population that is overweight, the ageing population and a more active society, the prevalence of articular cartilage damage is increasing [8].

CarGel, a chitosan-based cartilage biomatrix implant has been listed on the Prostheses List since August 2015, and have been reimbursed through the MBS since 2016, primarily using MBS item 49561 for repair of cartilage defects of the knee. **It is noted that the SOCAG/PLAC specified that this application (MSAC 1569) focus on the repair of focal cartilage defects of the knee, and the MBS item number 49561.** The exact number of patients with radiologically confirmed ICRS Grade 3 or 4 articular cartilage damage is difficult to confirm because there is no specific MBS item number associated with repair of cartilage. Given the request to focus on MBS 49561, an estimate can be calculated by determining by the number of patients receiving microfracture under MBS 49561 (arthroscopic surgery of the knee), involving one or more of: partial or total meniscectomy, removal of loose body or lateral release; where the procedure includes associated debridement, osteoplasty or chondroplasty - not associated with any other arthroscopic procedure of the knee region.

Utilisation of MBS item 49561 over time is provided in Figure 2. The graph suggests introduction of chitosan-based cartilage biomatrix implant in 2015 has not resulted in increased utilisation of MBS item 49561. In fact, the number of services claimed for this item decreased from 49,278 in 2014, to 34,566 in 2017 (and data released since MSAC Application 1569 was submitted shows a further decline). However, given MBS item descriptor 49561 is not limited to microfracture, it is unclear what proportion of utilisation of this item is directly relevant to microfracture, making interpretation of MBS utilisation data difficult.

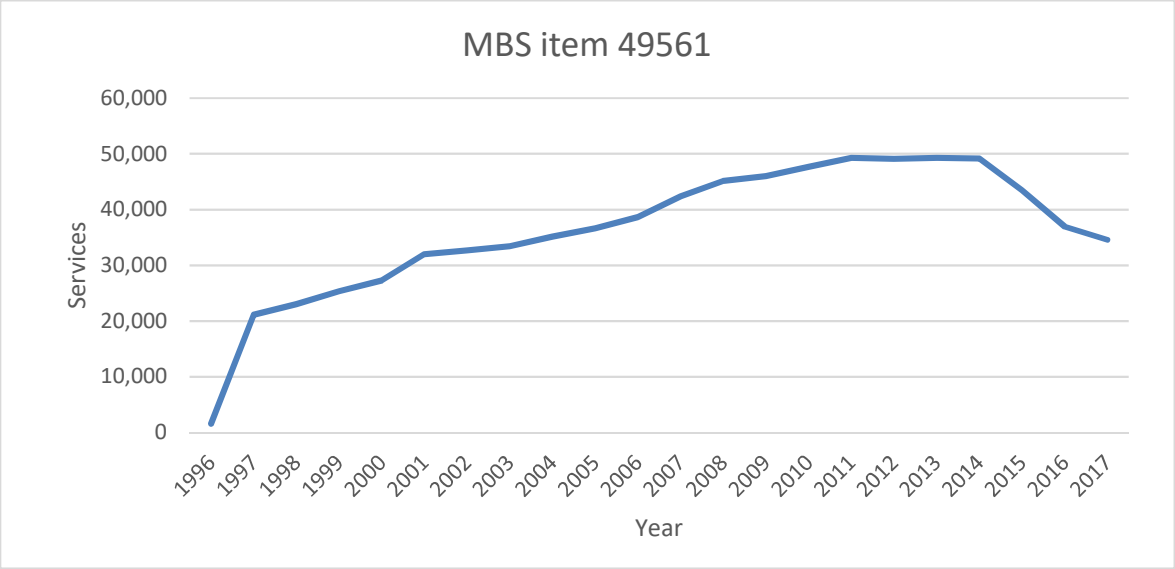

Figure 2 Utilisation of MBS item 49561 over time (1996-2017)
Source: MSAC Application 1569, Figure 1, p. 22; MBS Statistics online, 1996-2017.

Utilisation data for the number of chitosan-based cartilage biomatrix implant units sold over time in Australia (for private patients in private or public hospitals) are available, but these are redacted in the MSAC application.

In 2017-18, 32,419 patients received treatment under MBS 49561, 15,617 of which were aged 15 to 54 (37 per cent female and 63 per cent male). It is not known how many of these received microfracture [14].

Rationale

The proposed indication limits access to this treatment based on lesion size, amongst other factors, including status of the subchondral endplate (for lesions ≥ 2 cm^2). These are important determinants of treatment. Lesion less than 2 cm^2 have different treatment options for those sized 2 cm^2 or over [4]. These include microfracture, ACI, or the proposed treatment (MF+CBI). For those with lesions ≥ 2 cm^2 who have an intact subchondral endplate, potential treatment options include microfracture, ACI, mosaicplasty or the proposed treatment (MF+CBI). Evidence supporting the use of MF+CBI is based on the pivotal prospective randomised clinical trial by **Stanish and colleagues.** This trial compares microfracture alone with MF+CBI in 80 patients aged between 18 and 55 years, with a single, symptomatic focal lesion on the femoral condyle [1]. Based on available clinical evidence from the single randomised controlled trial in 80 patients [1], chitosan-based cartilage biomatrix implant in conjunction with microfracture is only recommended for lesions < 10 cm^2 [1, 15, 16].

This upper limit of lesion size (10 cm^2) should be considered as a threshold for eligibility by the PICO Advisory Sub-Committee (PASC). The largest lesion filled within the pivotal paper by Stanish and colleagues was 6.77 cm^2 [1], and 6 cm^2 in the supportive prospective non-randomised study (n=13) by Tahoun and colleagues [15].

The proposed indication limits access to this treatment to patients who are aged 15 to 55 years. This is based on the clinical evidence available witthat has only trialled this treatment in patients under this age and supported by Australian clinical expert advice [1]. In the pivotal randomised clinical trial by **Stanish and colleagues** (n=80), the inclusion criteria were as listed in Table 1.

A number of additional exclusion criteria were used in the pivotal randomised controlled trial by Stanish and colleagues – of particular note were limitation to a body mass index (BMI) of 30 kg/m^2 or less. However, PASC has advised that ARTG listing criteria is sufficient, without a BMI limit.

Table 1 Inclusion and exclusion criteria employed in the randomised controlled trial (RCT) assessing MF±CBI

TABLE E-1 Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Patients understood and signed a research ethics board-approved informed consent.	Patients had multiple lesions or kissing (opposing) lesion(s) of the condyle and tibia.
Patients had at least moderate knee pain (>4 points on a VAS from 0 to 10).	Patients had clinically relevant compartment malalignment (>5°).
Patients had a single lesion in the articular cartilage of the medial or lateral femoral condyle.	Patients had bone cyst(s) associated with, or adjacent to, the index lesion.
The lesion was up to 10 cm^2 in size.	Patients had osteochondritis dissecans with bone or bone-cartilage fragment in place.
The index lesion was classified as focal, full-thickness grade 3 or 4 according to the International Cartilage Repair Society score or grade III or IV according to the Outerbridge score.	Patients had ligament treatments in the index knee within the previous two years.
The index knee was stable (<5-mm side-to-side difference on Lachman and varus and valgus stress testing and grade 0 or 1 on the pivot-shift test), and the meniscal rim was intact.	Patients had surgical cartilage treatments in the index knee within the previous twelve months.
Patient age was between eighteen and fifty-five years.	Patients had intra-articular injections in the index knee within the previous two months.
Patients agreed to follow the recommended physiotherapy regimen, including exercises to be completed at home.	Patients had a body mass index (BMI) of >30 kg/m^2.
Patients agreed to not become pregnant or father a child for four months following surgery.	Patients had an autoimmune disease or a hypersensitivity to shellfish.
Patients agreed to discontinue the use of all knee pain medication seven days before the pretreatment visit and the posttreatment follow-up visits at three, six, and twelve months.	Patients had concomitant healing bone fractures.
	Patients had noteworthy pain in the ipsilateral hip or ankle or contralateral hip, knee, or ankle.
	Patients were pregnant or nursing.
	Patients had inflammatory arthropathy.
	Patients had blood clotting disorders, were receiving anticoagulant therapy, or had recurring deep vein thrombosis.
	Patients had a serious heart condition or liver and/or renal abnormalities diagnosed within the previous two years.
	Patients had chronic infection of the lower joint extremities.
	Patients had a history of alcohol or drug abuse within the previous twelve months.
	Patients had any medical condition that would, in the opinion of the investigator, render the patient unable to complete the study.

Source: Extracted from Stanish et al. (2013) [1]
CBI = chitosan-based cartilage biomatrix implant; MF = microfracture; RCT = randomised controlled trial

Patients with osteoarthritis, inflammatory polyarthropathy or those with joint instability are not recommended for this MF±CBI. However, patients who had joint instability that was rectified surgically, will be eligible for the procedure.

Prior test (investigative services only - if prior tests are to be included)
Not applicable. This application is for a 'therapeutic service'.

Intervention

PASC noted the PICO states the intervention is a once-in-a-lifetime procedure. However, PASC provided further clarification that it is once per lesion, not once per patient.

PASC noted that, while the knee is the most common site for this procedure, it is used in other parts of the body. However, PASC recommended the PICO and subsequent health technology assessment be restricted to the knee, given most evidence relates to this site.

Intervention	Chitosan-based cartilage biomatrix implant in conjunction with microfracture (CBI+MF) (also known as augmented microfracture). For the purpose of this PICO and subsequent health technology assessment, the intervention is restricted to lesions in the knee, and may be used once per lesion (not once per patient).

The intervention is chitosan-based cartilage biomatrix implant performed in conjunction with microfracture (CBI+MF) commonly termed 'augmented microfracture'. The patient receives the procedure under general anaesthesia, as an inpatient (admitted patient) in a public or private hospital, or as an admitted patient at a day surgery centre [1]. *Length of anaesthesia required was not provided in the application.*

The majority of procedures are performed in the official hospital inpatient setting, with patients staying overnight. A small proportion are performed in the day surgery setting, but also as admitted patients (*specific proportions occurring in the hospital versus day surgery inpatient/admitted-patient settings were not provided in the application).*

Given the procedure is restricted to inpatient/admitted patient settings (in either an official hospital or day surgery centre), there is no Extended Medicare Safety Net (EMSN) risk. EMSN risk only applies to out-of-hospital (i.e. non-admitted-patient) services.

The procedure is performed by orthopaedic surgeons. No additional training is required to apply the chitosan-based cartilage biomatrix implant in conjunction with microfracture.

Microfracture is performed under general anaesthesia arthroscopically, using an arthroscopic awl, with multiple holes or microfractures being made in the defect 3-4 mm apart. The chitosan-based cartilage biomatrix is applied through a mini-arthrotomy (i.e. mini-incision) [1]. The microfractured lesion is swabbed with a gauze to create a 'dry field' before a 3:1 mixture of fresh autologous whole peripheral blood:BST-CarGel is applied in a dropwise manner, using a syringe [1].

The volume applied depends on size of the patient's lesion (no information on volume used was supplied in the pivotal studies). A fifteen-minute waiting period allows the implant to clot in situ, and then the incision is closed. Patients then undergo a physiotherapy rehabilitation program, including 6 weeks of non-weight bearing. Jumping or pivoting is not permitted for 12 months.

Costs associated with providing chitosan-based cartilage biomatrix implantation in conjunction with microfracture are detailed in Table 2 below.

Table 2 Costs associated with providing chitosan-based cartilage biomatrix implantation in conjunction with microfracture for cartilage defect repair of the knee

Row	Parameters	Cost	Source/calculation
A	Chitosan-based cartilage biomatrix implant (CarGel)	$6,022	Prostheses list SL072
B	Pre-anaesthesia consultation	$43.65	MBS item 17610
C	Initiation anaesthesia	$79.20	MBS item 21382
D	Arthroscopic surgery, including use of chitosan-based cartilage biomatrix implant	$674.00	MBS item 49561 (inpatient/admitted patient only service)*
E	Anaesthesia	$79.20	MBS item 21382
F	**TOTAL**	**$6,898**	A+B+C+D+E

* Note: A number of other MBS items relate to cartilage repair, see Table 3.

The proposed service is dependent on the use of a prosthesis, which is already included on the Prostheses List:

Billing code(s): SL072
Trade name of prostheses: BST-CarGel
Clinical name of prostheses: chitosan-based liquid bioscaffold
Other device components delivered as part of the service: N/A
Cost of prosthesis: $6,022

The device is listed on the Australian Register of Therapeutic Goods (ARTG):

ARTG listing, registration or inclusion number: 298453, 252732
TGA approved purpose(s), if applicable: "CarGel is a medical device intended to promote hyaline cartilage regeneration when used in conjunction with the bone marrow stimulation technique for the repair of focal articular cartilage lesions. Treatment with CarGel should be performed by an orthopaedic surgeon".

Rationale

The size of cartilage defect is a determinant factor in the management of lesions (see Figure 4). Given the physiology of cartilage in articular joints are the same [17], it is anticipated that surgical management of any articular joint would follow the same guidance. However, there is no evidence for efficacy of MF+CBI in joints other than the knee.

The use of MF+CBI is a once-in-a-lifetime procedure **per lesion**. That is, patients who have had a previous MF+CBI procedure performed on a specific lesion would be ineligible to have the procedure performed on that lesion again. They may be eligible for other MF+CBI procedures on different lesions (if those lesions are eligible). **The Australian clinical expert advice indicated that treatment would be limited to single use per lesion.**

PASC clarified the intervention is a once per lesion intervention , not once per patient, and the PICO and subsequent health technology assessment should be restricted to the knee, given most evidence relates to this site.

Comparator

PASC agreed that microfracture is the primary comparator for both populations (i.e. smaller and larger lesions).

PASC noted that, in patients with larger lesions of > 2 cm^2 (Population 2), BST Cargel would only be used if these patients have an intact subchondral endplate. Patients with larger lesions who do not have an intact subchondral endplate are indicated for joint replacement. PASC therefore agreed the comparator for Population 2 should be microfracture.

This also ensures some comparator consistency between application 1569 and similar current application 1578.

PASC suggested the applicant could also include near-to-market comparators, if these exist. However, PASC acknowledged sufficient data may not be available.

In relation to mosaicplasty, the applicant reiterated advice provided to PASC by the applicant's nominated clinical expert that mosaicplasty is rarely used in Australia, because it is a technically difficult procedure to perform. The applicant suggested mosaicplasty is not a suitable comparator for Population 2.

PASC queried if earlier MSAC application 1140 (Matrix-induced Autologous Chondrocyte Implantation [MACI] and Autologous Chondrocyte Implantation [ACI]), was relevant to application 1569 (and similar current application 1578). MSAC considered MACI and ACI in 2011 (as alternatives to mosaicplasty and microfracture), but did not support public funding for these interventions.

Since the PASC meeting, the Department advised that, while MACI, ACI, mosaicplasty, plus other scaffold products available in Australia are not comparators for the product in application 1569 (or the product in similar application 1578), the assessment reports for application 1569 (and similar application 1578) should clearly detail the evidence (or lack thereof) for these and newer interventions against the product in application 1569 (and similar product in application 1578). This is for completeness, and to ensure robust information is available if MSAC wants to consider it.

Comparator	Population 1: Microfracture alone, in conjunction with standard of care Population 2: Microfracture alone, in conjunction with standard of care

Currently, patients with focal cartilage defects are treated according to size of their lesion. Those with small lesions undergo microfracture alone. The procedure is identical to that described above, except there is no use of chitosan-based cartilage biomatrix, therefore microfracture alone is considered the appropriate comparator for this patient population (with lesion < 2 cm^2).

In lesions >2 cm^2, the treatment is based on status of the subchondral endplate. In lesions with intact endplate, microfracture, ACI and mosaicplasty are potential treatment options (see Figure 4). However, mosaicplasty is rarely used in Australia, because it is a technically difficult procedure to

perform. ACI is rarely used in the private setting, due to the absence of MBS funding. Therefore, microfracture alone, which is a treatment option for patients with lesions > 2 cm^2, is considered the main comparator.

The applicant advised that, if left untreated, cartilage injuries can become degenerative and lead to premature early arthritis, affecting activities of daily living. PASC noted that, in the present case, being left untreated (or 'watchful waiting') is not the comparator.

Rationale

The current treatment pathway is highlighted in Figure 4. Advice provided to the applicant by the MSAC's clinical adviser suggested that while ACI is funded in the public setting, it is rarely performed. Microfracture is routinely performed in both public and private settings and is funded (see above).

ACI is a technique that involves the cultivation of chondrocytes in-vitro, using a two-stage operative approach, that is, patients require two separate episodes of hospital admission and surgical intervention, which occurs over a period of 8-12 weeks. The objective of the procedure is to replace damaged cartilage with hyaline cartilage. MACI, an alternative to ACI, has been removed from the market in Australia and is not considered further here.

Osteochondral autograft transfer (OAT), more commonly referred to as mosaicplasty, is used in focal defects (ineffective in degenerative defects) and is optimal in young patients with medium-sized lesion (2.5-4 cm^2) [18]. In this technically-demanding procedure, craters (that are bored into cartilage and bone of the damaged area) are filled with cartilage and bone plugs removed from healthy, non-weight-bearing areas of the joint [2]. Mosaicplasty is rarely used in Australia.

Microfracture procedures are currently funded in Australia under a number of MBS items, including item 49561 (see Table 3). However, it is not clear what proportion of the various MBS items is directly relevant to microfracture. It is noted that SOCAG/PLAC specified the application should focus on repair of focal cartilage defects of the knee, and MBS item 49561. The MBS items associated with the comparators are listed in Table 3.

Table 3 MBS items relating to potential comparators for MF+CBI

MBS item #	Descriptor	Fee	Services 2017 (Jan-Dec)
49500	KNEE, arthrotomy of, involving 1 or more of; capsular release, biopsy or lavage, or removal of loose body or foreign body	$376.55	1,419
41512	MEATOPLASTY involving removal of cartilage or bone or both cartilage and bone, not being a service to which item 41515 applies	$585.90	564
49557	KNEE, diagnostic arthroscopy of (including biopsy, simple trimming of meniscal margin or plica) - not being a service associated with autologous chondrocyte implantation or matrix-induced	$272.95	479

	autologous chondrocyte implantation or any other arthroscopic procedure of the knee region		
49558	KNEE, arthroscopic surgery of, involving 1 or more of: debridement, osteoplasty or chondroplasty - not associated with any other arthroscopic procedure of the knee region	$272.95	710
49559	KNEE, arthroscopic surgery of, involving chondroplasty requiring multiple drilling or carbon fibre (or similar) implant; including any associated debridement or oestoplasty - not associated with any other arthroscopic procedure of the knee region	$408.70	71
49560	KNEE, arthroscopic surgery of, involving 1 or more of: partial or total meniscectomy, removal of loose body or lateral release - not being a service associated with any other arthroscopic procedure of the knee region	$551.60	2,616
49561	KNEE, ARTHROSCOPIC SURGERY OF, involving 1 or more of: partial or total meniscectomy, removal of loose body or lateral release; where the procedure includes associated debridement, osteoplasty or chondroplasty - not associated with any other arthroscopic procedure of the knee region	$674.00	34,566
49562	KNEE, ARTHROSCOPIC SURGERY OF, involving 1 or more of: partial or total meniscectomy, removal of loose body or lateral release; where the procedure includes chondroplasty requiring multiple drilling or carbon fibre (or similar) implant and associated debridement or osteoplasty - not associated with any other arthroscopic procedure of the knee region	$735.50	3,278
49563 *This is the item most commonly associated with mosaicplasty*	KNEE, arthroscopic surgery of, involving 1 or more of: meniscus repair; osteochondral graft; or chondral graft (excluding autologous chondrocyte implantation or matrix-induced autologous chondrocyte implantation) - not associated with any other arthroscopic procedure of the knee region	$796.70	1,492
49503	KNEE, partial or total meniscectomy of, repair of collateral or cruciate ligament, patellectomy of, chondroplasty of, osteoplasty of, patellofemoral stabilisation or single transfer of ligament or tendon	$489.55	210

	(not being a service to which another item in this Group applies) - any 1 procedure		
49506	KNEE, partial or total meniscectomy of, repair of collateral or cruciate ligament, patellectomy of, chondroplasty of, osteoplasty of, patellofemoral stabilisation or single transfer of ligament or tendon (not being a service to which another item in this Group applies) - any 2 or more procedures	$734.40	330
Not listed	AUTOLOGOUS CHRONDOCYTE IMPLANTATION and MATRIX-INDUCED AUTOLOOUS CHRONDOCYTE IMPLANTATION[a]	Not listed	

[a] "An item in the range 1 to 10943 does not apply to the service described in that item if the service is provided at the same time as, or in connection with, any of the services specified below: … (n) autologous chondrocyte implantation and matrix-induced autologous chondrocyte implantation" - from the Medicare Benefits Schedule [19].

Outcomes

PASC recommended the addition of other long-term outcomes; specifically 'time to return to work' and 'total joint replacement/subsequent procedures'. However, PASC agreed there may be no evidence for these, given their long-term nature.

PASC recommended the Outcomes in application 1569 (and similar current application 1578) be consistent, where data is available.

Outcomes	<u>Clinical effectiveness</u> • Quality, quantity and structure of cartilage (quantity hyaline characteristic cartilage; proportion of lesion fill) • OMERACT (Outcome Measures in Rheumatology) • Time to weight bearing • Symptoms and function • Quality of life and patient satisfaction • WOMAC score • Tegner Activity Scale • International Cartilage Repair Society (ICRS) Score • Lysholm Knee Scoring Scale <u>Safety</u>: Adverse events and serious adverse events related to treatment; Treatment failure (defined as percentage lesion fill < 70%) <u>Cost-effectiveness:</u> Resource use: surgical costs (surgical time, surgeon consult, including for total joint replacement/subsequent procedures), days as an inpatient, inpatient paramedical consults (e.g. physiotherapy), medical devices (e.g. knee brace), laboratory tests, diagnostic tests (including MRI, X-ray, computed tomography (CT), CT angiography (CTA), follow-up physiotherapy rehabilitation, medication for pain management, indirect costs (time to return to work, work days lost, health related quality of life), quality-

	adjusted life years (QALY). Data limitations may inhibit consideration of longer-term outcomes, such as time to return to work, and total joint replacement/subsequent procedures. Data permitting, longer term outcomes should be considered.

Rationale

Patient-relevant outcomes

In the pivotal RCT by **Stanish and colleagues**, outcomes of interest included both structural outcomes, and patient-reported outcomes [1]. Outcomes were assessed at one-, three-, six- and 12 months post-treatment [1]. The co-primary endpoints, repair cartilage quality defined by the degree of lesion filling and the quality of new repair cartilage, were measured at 12 months [1]. The applicant noted, however, that significant improvements in the degree of lesion filling and the quality of new repair cartilage were likely to be seen at three months, and this time-point should also be assessed.

Figure 3 Recommended clinical and structural outcomes from Frappier et al [20], and additional recommended outcomes for consideration in the application

Structural outcomes	Patient reported outcomes	Safety	Cost-effectiveness
• Repair tissue quantity (lesion % fill) • Quality (T2 relaxation time) • Tegner activity scale • ICRS score • Lysholm score	• Clinical benefit measured using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) VAS version25, consisting of three subscales: pain, stiffness, and physical function • Quality of life (SF-36)	• Adverse events • Device-related adverse events • Serious adverse events • Treatment failure defined as lesion % fill < 70%*	• Hospitalisation • Surgical time • Surgeon consult • Paramedical consults (e.g. physiotherapy) • Medical devices (e.g. knee brace) • Laboratory tests • Diagnostic tests (including MRI, X-ray, electrocardiogram (ECG))[a] • Pain management • Indirect costs (work days lost) • HRQL

Source: Frappier and colleagues (2014) [20]. Note: * The percentage lesion fill in Frappier was assumed in the analysis as the threshold for inferring treatment failure and was based on the gradations of cartilage repair fill reported by Mithoefer and colleagues ((good: 67–100% fill; moderate: 34–66% fill; poor: 0–33% fill) and validated by the Delphi panel [21]. This was based on the gradations of cartilage repair reported by other authors. aECG assessment was included as part of the diagnostic work up in Frappier et al.

To ensure consistency with similar current application 1578, PASC recommended OMERACT (Outcome Measures in Rheumatology) and 'time to weight bearing' be added to application 1569's outcomes.

Another potentially-relevant outcome is patient satisfaction, although this was not measured in the pivotal study.

The clinical adviser suggested the risk of premature arthritis, and subsequent total joint replacement (TJR), was not an outcome of interest for this reason. However, premature arthritis and total joint replacement (or total knee replacement (TKR)) should be considered if the evidence suggests that the efficacy of MF+CBI delays these events and their associated costs, relative to microfracture alone.

Treatment failure, defined as lesion fill < 70% [20], is also an important endpoint, and this has been added to the table above. The percentage lesion fill in **Frappier** was assumed in the analysis as the threshold for inferring treatment failure, and was based on gradations of cartilage repair fill reported by Mithoefer and colleagues (good: 67–100% fill; moderate: 34–66% fill; poor: 0–33% fill) and validated by the Delphi panel [21]. Treatment failure with MF±CBI is likely to lead to a second surgery, such as autologous chondrocyte implantation (ACI), which if failed, may lead to a total joint replacement [20]. Long-term (5-year) efficacy, including structural and clinical outcomes, and safety data from the cohort enrolled in the **Stanish** trial [1] have been published by **Shive and colleagues** [22]. There were 67 of the original 80 patients enrolled in the extension study, but their enrolment was distributed across the 5-year study period: data were available from only four patients (5%) at two years, 32 patients (40%) at three years, 47 (59%) at four years, and 60 (75%) at five-year follow-up. Only two patients had complete data for one, two, three, four and five years [22]. Blinded MRI analysis demonstrated that MF+CBI-treated patients showed a significantly greater treatment effect for lesion filling ($p = 0.017$) over 5 years compared with microfracture alone. A significantly greater treatment effect for MF+CBI was also found for blinded MRI analysis of repair tissue T2 relaxation times ($p = 0.026$), which were closer to native cartilage compared to the microfracture group.

MF+CBI and microfracture groups showed highly significant improvement at 5 years from pre-treatment baseline for each WOMAC subscale ($P < 0.0001$), and there were no differences between treatment groups. Safety was comparable for both groups. However, it is important to note that a significant proportion (25%) of patients were lost to follow-up [22].

Cost-effectiveness outcomes

Based on the Frappier analysis [20], the recommended cost-effectiveness endpoints include resource use: hospitalisation, surgical time, surgeon consults, paramedical [allied health] consults (e.g. physiotherapy), medical devices (e.g. knee brace), laboratory tests, diagnostic tests (including MRI, X-ray, ECG), pain management, indirect costs (work days lost), and impacts on health-related quality of life. It is acknowledged that data limitations may inhibit consideration of longer-term outcomes, such as time to return to work, and total joint replacement/subsequent procedures. Data permitting, longer term outcomes should be considered.

Current and proposed clinical management algorithm for identified populations

The current and proposed clinical management algorithm for the identified populations is shown in Figure 4.

PASC noted the algorithm reflected that the subchondral endplate must be intact for Population 2 (larger lesions > 2 cm^2).

PASC advised that the algorithms for application 1569 (and similar current application 1578) should be consistent as far as possible (acknowledging that the algorithms for larger lesions will be different).

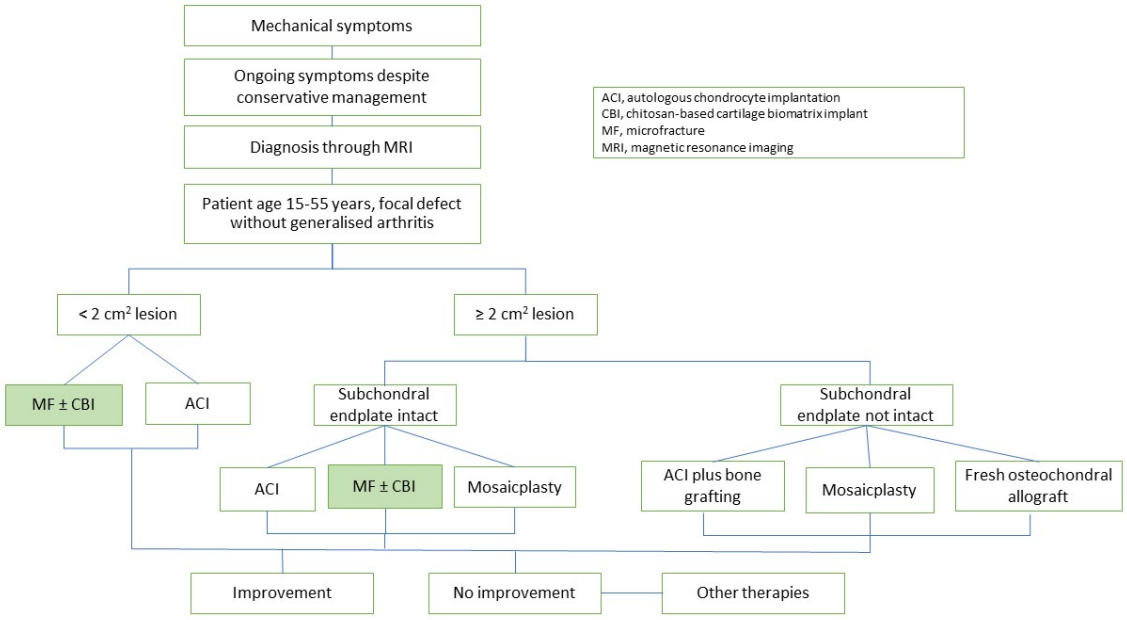

Figure 4 Current and proposed clinical management algorithm for identified population

Note: ACI = autologous chondrocyte implantation; CBI = chitosan-based cartilage biomatrix implant; MF=microfracture; MRI=magnetic resonance imaging
The current treatment algorithm is in white, with additions proposed in green.
Source: Applicant, Appendix A.

Proposed economic evaluation

Based on Stanish et al 2013 [1], the clinical claim is that, compared with microfracture in conjunction with standard care, the use of a chitosan-based cartilage biomatrix implant in conjunction with microfracture results in superior outcomes. Combined with the applicant's claim of superiority, the comparative clinical claim for the assessment is superiority, which requires cost effectiveness analysis (CEA) or cost utility analysis (CUA).

PASC confirmed a cost-effectiveness analysis (CEA) or cost-utility analysis (CUA) should be conducted, given the clinical claim is that the technology is superior to the comparator (microfracture).

Table 4 Classification of the comparative effectiveness and safety of chitosan-based cartilage biomatrix implant (BST-CarGel), in conjunction with the marrow stimulation technique (microfracture) and guide to the suitable type of economic evaluation

Comparative safety	Comparative effectiveness			
	Inferior	Uncertain[a]	Non-inferior[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

Non-inferior[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 'non-inferiority' is the preferred basis for demonstrating equivalence

The main health economic gains or losses for the treatment of cartilage defects lie in the longer term when osteoarthritis develops, potentially leading to a total joint replacement (TJR).

Given evidence that tissue quality and improved cartilage repair are predictors of improved clinical symptoms and long-term durability, it is appropriate to consider outcomes more than five years from the intervention. For this reason, a timeframe of 10 years is recommended for the economic evaluation, even though MBS impacts do not need to be considered for this duration.

Microfracture alone in conjunction with standard of care should be the comparator for the economic evaluation.

A summary of the proposed characteristics of the economic evaluation is given in Table 5.

Table 5 Summary of the economic evaluation

Perspective	Australian healthcare system
Comparator	Microfracture alone in conjunction with standard of care
Type of economic evaluation	Cost effectiveness analysis (or cost-utility analysis depending on evidence)
Sources of evidence	RCT, observational studies
Time horizon	10 years
Outcomes	Structural outcomes, functional outcomes, quality adjusted life years, working days lost
Methods used to generate results	Markov model

Given that lesion size is a predictor of cascading events (subsequent health status and required interventions) [18], the economic evaluation should separately identify costs and outcomes on the basis of lesion size. Therefore, lesion size should form the basis of a risk based approach to the economic evaluation: both in terms of the likelihood of cascading events, as well as costs and outcomes of treatment.

Hence, where possible, the economic evaluation approach should consider predictors of treatment failure and risks of longer term (more than five years) outcomes related to the durability of different types of cartilage repair and the utility associated with each type for particular patient groups (patient age by lesion size).

This means including in the economic evaluation:

- patient age, defect size
- treatment failure for the comparator and intervention
- structural outcomes
    - the expected delay in osteoarthritis (distinguishing between mild and severe OA)

    - the expected delay or avoidance of total joint replacement (likely associated with delay of severe OA)
- functional outcomes (daily activities such as work) and pain (including requirements for pain relief)
- need for further surgery under the comparator and intervention (considering expected predictors or future procedures
- quality of life
    - utility scores for OA (mild and severe) and the utility following TJR
    - quality adjusted life years associated with repaired cartilage defect and that of cartilage damage, and
- productivity impacts (work days lost).

This proposed approach is illustrated in Figure 5, which recommends assessment (or consideration of probabilities) of cascading events associate with lesions above and below 2cm^2, and the risks of OA being mild, severe, and/or requiring TJR. Figure 5 and Table 5 provide the framework for the economic evaluation.

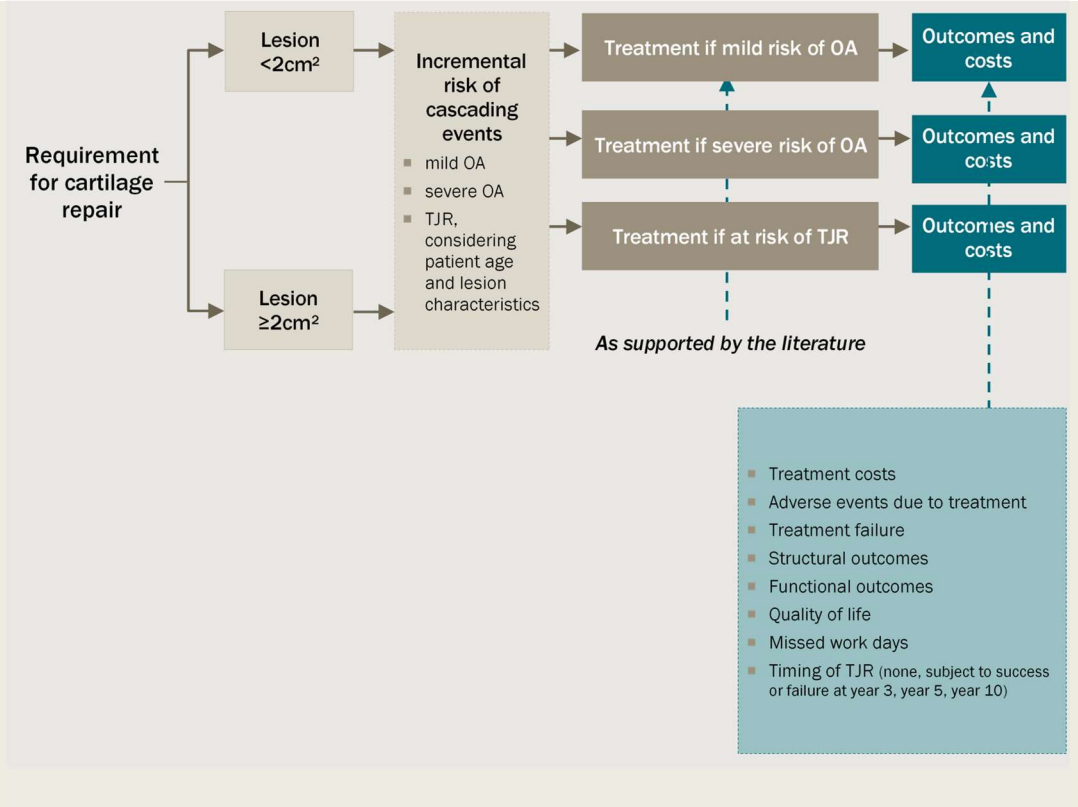

Figure 5 Proposed risk-based approach to the economic evaluation
Source: Centre for International Economics.

Cost estimates should include:

- MRI scanning and other laboratory and diagnostic tests
- total surgical costs:
    - surgical consultation time
    - Chitosan-based cartilage biomatrix implant (CarGel)
    - pre-anaesthesia consultation

    - initiation anaesthesia
    - arthroscopic surgery
    - anaesthesia
    - days as an inpatient
    - surgical visits post-surgery
- post treatment follow-up physiotherapy rehabilitation
- pain management (pain medications used, pain management surgeries)
- medical devices (including knee brace)
- adverse events (mild, moderate, and severe intensity)
- productivity costs, possibly measured as missed work days, and
- health-related quality of life (HRQoL).

The applicant stated that costs associated with a knee brace are not required for the comparator. According to the applicant, 'Patients who have received chitosan-based cartilage biomatrix implant in conjunction with microfracture require a knee brace for a short time to immobilise the joint immediately after the procedure to prevent the gel from being displaced. Patients undergoing microfracture alone do not require a knee brace'.

This approach to the economic evaluation is in line with the economic evaluation framework used by Frappier et al. 2014 [15], although we have included HRQoL, which has been adopted in other relevant studies [17].

Sensitivity analysis may be useful for key variables such as:

- failure rates to assess when the intervention becomes cost effective (assuming there is no long term impact on avoided TJR)
- time (duration) to TJR for severe OA
- longer-term health related quality of life gains from the intervention, and
- the discount rate used (assuming longer-term impacts are identified).

Proposed item descriptor

The applicant did not propose a specific MBS item descriptor (or wording to amend an existing item), but awaits discussions with the Department on the preferred approach (e.g. new MBS item; amendment to an existing MBS item; or using an unamended existing MBS item). Similarly, a proposed MBS fee was not proposed by the applicant.

The applicant has acknowledged there are several potential MBS items that may be used for cartilage repair of the knee, and it is not clear which of these items are directly relevant to MF $\pm$ CBI.

PASC noted current MBS item (49561) includes a range of procedures associated with the knee. Out of the approximately 34,000 services performed in 2017, it is unclear how many are for microfracture. The estimate is around 300 services in the private sector (i.e. others may be provided to patients electing to be private patients in the public sector). MBS items only relate to private services.

PASC noted the proposed descriptor in the PICO document reflects the trial population, being very specific. PASC questioned whether the item descriptor should be broad, for cartilage biomatrix implants in conjunction with microfracture.

PASC concluded that MSAC may decide to recommend a generic MBS item descriptor, if that is most appropriate.

PASC advised it is unclear how the $6,022 benefit had been determined (calculated) for the Prostheses List.

PASC also noted that PLAC can place conditions/criteria on a prosthesis listing (e.g. age-range, joint), independent of what the MBS item descriptor states.

One approach is to amend existing MBS item 49561, to allow the proposed intervention to be billed under that item. The current fee for MBS item 49561 is $675.

A cost-reflective MBS fee should be set at no less than $675, as determined by MSAC, following further input from the applicant.

Category (proposed category number) – (proposed category description)
The applicant will provide further advice on the proposed MBS item descriptor and MBS fee during the assessment phase. For the purpose of the PICO, the proposed item descriptor and fee are: Chitosan-based cartilage biomatrix implant in conjunction with microfracture in **Population 1:** Patients with radiologically confirmed International Cartilage Repair Society (ICRS) Grade 3 or 4 articular cartilage defect ≤ 2 cm^2 with moderate knee pain **Population 2:** Patients with radiologically confirmed International Cartilage Repair Society (ICRS) Grade 3 or 4 articular cartilage defect > 2 cm^2 with an intact subchondral endplate and with moderate knee pain. Patients in Population 1 or Population 2 who are ineligible for treatment are those who: 1. have evidence of advanced osteoarthritis in the joint of interest, or have generalised osteoarthritis; OR 2. have an inflammatory arthropathy, for example, rheumatoid arthritis, psoriatic arthritis; OR 3. have significant articular instability in the joint in question, for example a ligament injury (patients who have had repairs to articular instability are not excluded). MBS Fee: Not less than $675 (to be further informed by the applicant)

Consultation feedback

PASC noted that no consultation feedback was received for application 1569.

However, PASC noted one piece of feedback was received from a peak medical professional organisation for similar current application 1578 – *Arthroscopic injection of a bioadhesive hydrogel implant, in conjunction with microfracture for treatment of osteochondral defects of the knee ('JointRep').*

Next steps

Once PICO 1569 is updated and ratified, the application can PROCEED to the pre-Evaluation Sub-Committee (ESC) stage, with the applicant electing to prepare its own ADAR (applicant-developed assessment report).

References

1. Stanish, W.D., et al., *Novel scaffold-based BST-CarGel treatment results in superior cartilage repair compared with microfracture in a randomized controlled trial.* J Bone Joint Surg Am, 2013. **95**(18): p. 1640-50.
2. Ozturk, A., M.R. Ozdemir, and Y. Ozkan, *Osteochondral autografting (mosaicplasty) in grade IV cartilage defects in the knee joint: 2- to 7-year results.* Int Orthop, 2006. **30**(3): p. 200-4.
3. Løken, S., et al., *Epidemiology of Cartilage Injuries*, in *Sports Injuries: Prevention, Diagnosis, Treatment and Rehabilitation*, M.N. Doral and J. Karlsson, Editors. 2015, Springer Berlin Heidelberg: Berlin, Heidelberg. p. 1-12.
4. Decogliano, M., J. Boyer, and B.R. Mandelbaum, *Patient evaluation and treatment algorithms*, in *Cartilage surgery: an operative manual*, M. Brittberg and W. Gersoff, Editors. 2011, Elsevier. p. 9-18.
5. Gomoll, A.H., et al., *Surgical management of articular cartilage defects of the knee.* J Bone Joint Surg Am, 2010. **92**(14): p. 2470-90.
6. Bhosale, A.M. and J.B. Richardson, *Articular cartilage: structure, injuries and review of management.* Br Med Bull, 2008. **87**: p. 77-95.
7. Cole, B.J., C. Pascual-Garrido, and R.C. Grumet, *Surgical management of articular cartilage defects in the knee.* J Bone Joint Surg Am, 2009. **91**(7): p. 1778-90.
8. Evans, C.H., S.C. Ghivizzani, and P.D. Robbins, *Orthopedic gene therapy in 2008.* Mol Ther, 2009. **17**(2): p. 231-44.
9. Aroen, A., et al., *Articular cartilage lesions in 993 consecutive knee arthroscopies.* Am J Sports Med, 2004. **32**(1): p. 211-5.
10. Curl, W.W., et al., *Cartilage injuries: a review of 31,516 knee arthroscopies.* Arthroscopy, 1997. **13**(4): p. 456-60.
11. Hjelle, K., et al., *Articular cartilage defects in 1,000 knee arthroscopies.* Arthroscopy, 2002. **18**(7): p. 730-4.
12. Aurich, M., et al., *Differences in injury pattern and prevalence of cartilage lesions in knee and ankle joints: a retrospective cohort study.* Orthop Rev (Pavia), 2014. **6**(4): p. 5611.
13. Logerstedt, D.S., et al., *Knee Pain and Mobility Impairments: Meniscal and Articular Cartilage Lesions Revision 2018.* J Orthop Sports Phys Ther, 2018. **48**(2): p. A1-A50.
14. Australian Government Department of Human Services. *Medicare Item Reports*. 2019 [cited 2019 25 March]; Available from: http://medicarestatistics.humanservices.gov.au/statistics/mbs_item.jsp.
15. Tahoun, M., et al., *Results of arthroscopic treatment of chondral delamination in femoroacetabular impingement with bone marrow stimulation and BST-CarGel((R)).* SICOT J, 2017. **3**: p. 51.
16. Tahoun, M.F., et al., *Arthroscopic Repair of Acetabular Cartilage Lesions by Chitosan-Based Scaffold: Clinical Evaluation at Minimum 2 Years Follow-up.* Arthroscopy, 2018. **34**(10): p. 2821-2828.
17. Rice University, *9.4 Synovial joints.*, in *Anatomy and Physiology. Available https://opentextbc.ca/anatomyandphysiology/chapter/9-4-synovial-joints/*.
18. Falah, M., et al., *Treatment of articular cartilage lesions of the knee.* Int Orthop, 2010. **34**(5): p. 621-30.
19. Australian Government Department of Health, *Medicare benefits schedule. http://www9.health.gov.au/mbs/search.cfm?pdf=yes. Accessed 25 March 2019.* 2019.
20. Frappier, J., et al., *Economic evaluation of BST-CarGel as an adjunct to microfracture vs microfracture alone in knee cartilage surgery.* J Med Econ, 2014. **17**(4): p. 266-78.
21. Mithoefer, K., et al., *Clinical efficacy of the microfracture technique for articular cartilage repair in the knee: an evidence-based systematic analysis.* Am J Sports Med, 2009. **37**(10): p. 2053-63.
22. Shive, M.S., et al., *BST-CarGel(R) Treatment Maintains Cartilage Repair Superiority over Microfracture at 5 Years in a Multicenter Randomized Controlled Trial.* Cartilage, 2015. **6**(2): p. 62-72.
23. Van der Meijden, O.A., T.R. Gaskill, and P.J. Millett, *Glenohumeral joint preservation: a review of management options for young, active patients with osteoarthritis.* Adv Orthop, 2012. **2012**: p. 160923.

Appendix

Table 6 ICRS lesion classification system

Grade	Details
0	Normal
1	Nearly normal – superficial lesions. A) Soft indentation and/or B) superficial fissures and cracks
2	Abnormal – lesion extending down to < 50% of cartilage depth
3	Severely abnormal – cartilage defects extending down > 50% of cartilage depth (A) as well as down to calcified layer (B) and down to but not through the subchondral bone (C)
4	Severely abnormal – with penetration through subchondral plate

Source: Van der Meijden et al (2012) [23]