Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1569 – Chitosan-based cartilage bio-matrix implant (BST-CarGel), in conjunction with the marrow stimulation technique (microfracture), for repair of focal cartilage defects.

Applicant: **Smith and Nephew Pty Ltd**

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

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

1.   Purpose of application

This application is in response to a request from the Prostheses List Advisory Committee (PLAC) for MSAC to provide advice on the comparative clinical and cost-effectiveness of BST-CarGel. To inform this consideration an applicant developed assessment report (ADAR) for CARGEL/BST-CarGel in conjunction with microfracture surgery (MF) for the repair of focal cartilage defects was received from Smith and Nephew by the Department of Health.

2.   MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC did not support public funding for chitosan-based cartilage biomatrix implant (CARGEL/BST-CarGel) in conjunction with microfracture (MF) surgery for the repair of focal cartilage defects. To inform the Prostheses List Advisory Committee (PLAC) consideration of the current listing for BST-CarGel on the Prostheses List (PL), MSAC will advise PLAC that BST-CarGel is not cost-effective as there is insufficient evidence to support non-inferior safety and superior effectiveness of BST-CarGel compared with MF alone.

Consumer summary
This application is in response to a request from the Prostheses List Advisory Committee (PLAC) for MSAC to perform a health technology assessment for BST-CarGel plus microfracture (MF). Specifically, MSAC was asked to review BST-CarGel's clinical effectiveness and cost-effectiveness when compared to MF alone, for the repair of cartilage defects. BST-CarGel has been on the Prostheses List (PL) since 2015.

Cartilage cushions the bones so that joints (such as the knee) can move easily. If cartilage is damaged, it cannot regenerate (regrow) on its own. If the damage is left untreated, it can |

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

MSAC noted that the purpose of this application is to determine whether BST-CarGel plus MF is more clinically effective and cost-effective compared with MF alone, and therefore whether it should remain on the PL. MSAC noted that BST-CARGEL has been reimbursed via the MBS and the Prosthesis List (PL) since August 2015, with the PL listing not limited by joint location. MSAC noted that the PICO Advisory Sub-committee (PASC) recommended the health technology assessment be restricted to the knee, to align with the available evidence.

MSAC noted two subpopulations were considered: symptomatic patients with radiologically confirmed grade 3 and grade 4 lesions either <2cm^2 (population 1) or ≥2cm^2 in size with intact subchondral endplate (population 2); and that these subpopulations were not analysed separately in the ADAR. MSAC also noted by definition, grade 4 lesions classified with the Internal Cartilage Repair Society (ICRS) classification system do not have an intact chondral endplate and thus the proposed indication cannot include grade 4 for either population 1 or 2.

MSAC noted the Evaluation-Sub-Committee (ESC) discussion for the clinical management algorithms, which indicated that MF surgery is appropriate for the treatment of knee cartilage lesions of up to 5cm^2 (expert advice), and that age and level of activity of the patient are important considerations, which are not included in the algorithm. MSAC also noted that MF plus other scaffolding products (with one such competitor product going through the MSAC process) were not included in the algorithm.

MSAC noted the lack of consumer response and that consultation feedback was limited to a response from a single clinician. This feedback considered that MF is harmful, reduces the effectiveness of other treatments and has been discredited as a therapeutic procedure.

MSAC also noted there is limited evidence that MF should be accepted as the gold standard for the treatment of chondral lesions of the knee (Erggelelet et al. 2016[1]).

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[1] Erggelet C, Vavken P. Microfracture for the treatment of cartilage defects in the knee joint–A golden standard?. Journal of clinical orthopaedics and trauma. 2016 Jul 1;7(3):145-52.

MSAC noted that the ADAR relied upon one randomised controlled trial (RCT) comparing BST-Cargel+MF *vs.* MF (Stanish et al. 2013) and two follow-up studies containing subsets of patients from this RCT; one looking at histological outcomes at 13 months and one looking at the structural and clinical outcomes at 5 years follow-up. MSAC noted:

- that the pivotal RCT was limited to assessment of structural and clinical outcomes over 12 months, and that the sponsor of the RCT was the company that owned BST-CarGel at the time and thus there were potential conflicts of interest with all three studies relating to associations with the sponsor.
- that the 5-year follow-up study had a high risk of selection bias owing to patient continuation in the study by choice and bias from a high loss to follow-up. Thus, MSAC considered the results from this study to be highly uncertain.

MSAC noted that the applicant claims non-inferior safety, but there was uncertainty due to serious adverse events being only reported in number and not their characteristics (5/41 patients). There was additional uncertainty due to the RCT using arthrotomy, whereas clinical practice generally employs arthroscopic access.

MSAC noted that the applicant claims superior clinical effectiveness based on significant improvement in structural outcomes as determined by magnetic resonance imaging (MRI). However, MSAC also noted that the effect size and 95% confidence interval (CI) failed to reach the pre-specified difference of 15% for the lesion fill outcome (see Table 4). In addition, MSAC noted that patient-reported outcomes assessing pain, stiffness and function (Western Ontario and McMaster Universities Arthritis Index [WOMAC]) and quality of life (Short Form 36 [SF-36]) did not differ significantly between BST-CarGel plus MF *vs.* MF alone. MSAC queried whether improvements in structural outcomes based on imaging are valid surrogates for improvement in patient symptoms.

MSAC noted the pre-MSAC response, in which the applicant provided supportive evidence of the correlation between MRI and clinical outcomes. However, MSAC noted a recent review by Branco da Cunha et al. 2020[2] (not included in the ADAR) which reported that imaging studies showed inconsistent results when using enhanced MF techniques. Thus, MSAC considered that the strength of the correlation between MRI and clinical outcomes remains highly uncertain.

Overall, MSAC considered the superior effectiveness claim was highly uncertain, and in particular over the longer term, for which there was an absence of reliable data.

MSAC noted the many uncertainties in health economic outcomes mainly due to uncertain clinical benefit, and the ADAR's assumptions that structural outcomes are correlated with clinical outcomes, no risk of subsequent treatment in the base case, and treatment success/failure is sustained for the duration of the model. In particular, MSAC considered the assumption which extrapolated the 12-month outcomes as maintained over a 20-year time horizon was highly unrealistic and did not align with independent expert advice indicating that MF is not considered a long-term cure with many patients going on to other procedures later in life. MSAC noted the Commentary's additional analyses including more realistic scenarios with regression of treatment effect and subsequent treatments resulted in much higher incremental cost-effectiveness ratios (ICERs) compared with the ADARs base case

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[2] da Cunha CB, Andrade R, Veloso TR, Learmonth DA, Espregueira-Mendes J, Sousa RA. Enhanced microfracture using acellular scaffolds improves results after treatment of symptomatic focal grade III/IV knee cartilage lesions but current clinical evidence does not allow unequivocal recommendation. Knee Surgery, Sports Traumatology, Arthroscopy. 2020 Jan 1:1-3.

model (see Table 8). MSAC also noted the pre-MSAC response, in which the applicant provided alternative data for treatment regression and retreatment with MF which resulted in lower ICERs (see Table 8). However, MSAC agreed with ESC and considered overall that there was a high level of uncertainty in the ICER, primarily due to poor-quality clinical data and the fact that it relied on structural MRI outcomes at 12-months.

MSAC noted that, because BST-CARGEL is already reimbursed continued listing has no budget implications. MSAC noted the pre-MSAC response indicating the recent **redacted** in CARGEL sales due to the listing of competitor product on the PL, which the applicant claimed would **redacted** MBS costs associated with the use of CARGEL with MF.

To inform the Prostheses List Advisory Committee (PLAC) consideration of the current listing for BST-CarGel on the Prostheses List (PL), MSAC will advise PLAC that BST-CarGel is not cost-effective as there is insufficient evidence to support non-inferior safety and superior effectiveness of BST-CarGel compared with MF alone.

MSAC recalled that other 'like' products (matrix-induced autologous chondrocyte implantation [MACI] and autologous chondrocyte implantation [ACI]) for the treatment of large (>2cm^2) chondral lesions of the knee were not supported due to the increased cost compared to existing procedures and the insufficient evidence of improvement in clinical outcomes ([MSAC application 1140 Public Summary Document 2010](#)).

Other discussion

MSAC noted that the decision to not support BST-CarGel may have implications for competitor products coming through the MSAC process.

4.   Background

This is the first submission for BST-CARGEL in <2 cm^2 (population 1) or ≥ 2 cm^2 in size with intact subchondral endplate (population 2). MSAC has not previously considered this application.

The ADAR stated that the use of CARGEL+MF is not limited by joint location and used in cartilage repair of other joints than just the knee – including hip and ankle with associated relevant MBS item numbers. PASC recommended the HTA *"be restricted to the knee, given most evidence relates to this site"*

CARGEL has been listed on the Prostheses List (PL) since August 2015. The billing code SL072 for CARGEL is associated with the MBS item code (49561) on the basis that CARGEL is considered to be similar to autologous chondrocyte implantation (ACI) and matrix-induced autologous chondrocyte implantation (MACI). ACI/MACI had been previously assessed by MSAC as not suitable for public funding (MSAC Application 1140 Public Summary Document [PSD], December 2010).

The Prostheses List Advisory Committee (PLAC) recommended a health technology assessment (HTA) via MSAC for CARGEL to determine the clinical effectiveness and cost-effectiveness of this product, and to clarify the appropriateness of MBS item 49561.

Other MSAC applications for chondral defects of the knee
MSAC application 1140 for matrix-induced autologous chondrocyte implantation (MACI) and autologous chondrocyte implantation (ACI) was considered by MSAC in 2010. MSAC did not support public funding for MACI or ACI for the treatment of chondral defects in the

knee and other joints, due to the increased cost compared to existing procedures and the lack of evidence showing short term or long-term improvements in clinical outcomes (MSAC application No. 1140 Public Summary Document 2010)

5.   Prerequisites to implementation of any funding advice

CARGEL is available in Australia and is listed on the Therapeutic Goods Administration (TGA) website under two numbers (Table 1).

Table 1 Chitosan-based materials available in Australia for cartilage repair as listed on the ARTG

Registered Item	Manufacturer	ARTG number	Date of introduction	Device category
CARGEL – Cartilage biomatrix implant	Smith & Nephew, Inc Endoscopy Division (Andover, MA, USA)	298453	11/01/2018	Medical Device Included Class III
BST-CarGel® – Cartilage biomatrix implant	Piramal Healthcare Canada Ltd, Bio-Orthopaedics Division (Quebec, Canada)	252732	05/08/2015	Medical Device Included Class III

Abbreviations: ARTG = Australian Register of Therapeutic Goods.
Source: Table 12, p 39 of the Commentary

6.   Proposal for public funding

The Applicant is committed to working with the Department to finalise a suitable item descriptor dependent on the preferred approach (new MBS item code, as suggested by PASC [Table 2], amended MBS item code, or unchanged MBS item code). The ADAR stated that the proposed fee for this service is identical to that of existing MBS item 49561.

Table 2   Proposed MBS item descriptor

Category 3 – Therapeutic procedures
MBS item #####
Arthroscopic surgery including application of chitosan-based cartilage biomatrix implant in conjunction with microfracture
Fee: $684.80 Benefit 75% = $$513.60

Source: Table 1, p17 of the ADAR

7.   Summary of public consultation feedback/consumer Issues

Consultation feedback was received from one clinician which advised that MF has been discredited as a therapeutic procedure as it is destructive, damaging and reduces the effectiveness of other treatments. The feedback also indicated that this view is supported in the recent scientific literature but no citations were provided.

8.   Proposed intervention's place in clinical management

Description of Proposed Intervention
The proposed medical service is insertion of CARGEL, in conjunction with the marrow stimulation technique (i.e. MF) for repair of focal cartilage defects. Using an arthroscopic awl, multiple holes or microfractures are made in the defect 3–4 mm apart. CARGEL is mixed with autologous whole blood and is applied to the microfractured cartilage lesion, where it physically stabilises the clot and guides and enhances marrow-derived repair to promote hyaline cartilage regeneration. The patient receives the procedure under general anaesthesia, as an inpatient (admitted patient) in a public or private hospital with patients

staying overnight, or as an admitted patient at a day surgery centre (Stanish 2013[3]). The procedure is performed by orthopaedic surgeons.

Description of Medical Condition(s)
Clinical workup is required to distinguish focal lesions of the articular surface from degeneration of cartilage occurring as a consequence of osteoarthritis. Articular cartilage lesions are predominantly present in weight-bearing joints such as knees and ankles and are usually caused by traumatic injury (Årøen et al. 2004[4]). Chondral lesions are usually observed in 11% to 66% of the knee arthroscopies conducted.

The population described in the ratified PICO confirmation comprises two subpopulations:
- Population 1: patients presenting symptomatic (i.e. moderate knee pain) and radiologically confirmed grade 3 and grade 4 lesions of either < 2 cm^2; or
- Population 2: patients presenting symptomatic and radiologically confirmed grade 3 and grade 4 lesions of ≥ 2 cm^2 in size with intact subchondral end-plate.

Patients were excluded from the PICO ratified population if they presented:
- lesions ≥ 2 cm^2 and damaged subchondral end-plate; OR
- proven advanced osteoarthritis either in the targeted joint or generalised; OR
- inflammatory arthropathy such as rheumatoid arthritis or psoriatic arthritis; OR
- a pre-existing significant articular instability such as ligament injury.

Place in clinical management
There are no official clinical guidelines in Australia for the management of chondral injuries. The current and proposed clinical management algorithm is provided in Figure 1.

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[3] Stanish, W. D., Mccormack, R., Forriol, F., Mohtadi, N., Pelet, S., Desnoyers, J., Restrepo, A. & Shive, M. S. 2013. Novel scaffold-based BST-CarGel treatment results in superior cartilage repair compared with microfracture in a randomized controlled trial. J Bone Joint Surg Am, 95, 1640-50.
[4] Aroen, A., et al., Articular cartilage lesions in 993 consecutive knee arthroscopies. Am J Sports Med, 2004. 32(1): p. 211-5.
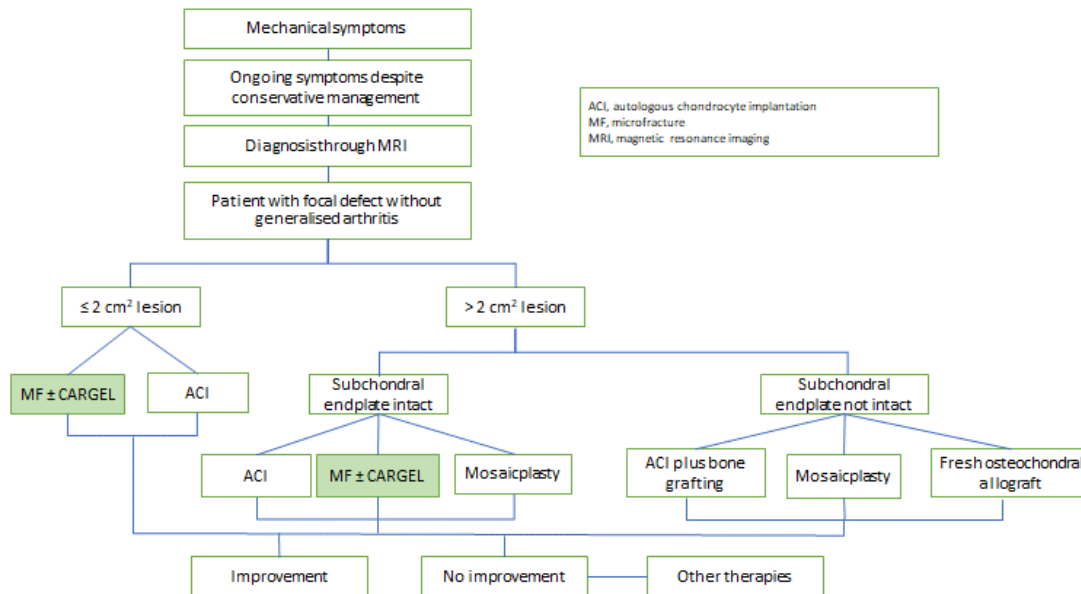
Figure 1 Current and proposed clinical management algorithm
ACI=autologous chondrocyte implantation; MF=microfracture; MRI=magnetic resonance imaging
The current treatment algorithm is in white, with additions proposed in green.
Source: Figure 1 of the ADAR. The algorithm was slightly modified. The ≥ sign in larger lesions was altered to >, and the < sign was altered to ≤ sign in smaller lesions, for consistency with PICO defined population. Also consistent with the stipulated population, the requirement that a patient must be 15-55 years old has been removed).

The Commentary analysed different published clinical management algorithms, stating that there are discrepancies on whether microfracture (MF) is recommended for cartilage lesions of either $< 2cm^2$ or $\geq 2cm^2$ in size. The clinical expert consulted by the reviewers stated that MF surgery is appropriate for the treatment of knee cartilage lesions of up to 5 cm^2 in size. Independent of the course of treatment chosen, all procedures need to be conducted by an orthopaedic surgeon. In addition, the applicants did not include in their algorithm the two major factors influencing the choice of a course of treatment for the management of knee focal cartilage repair: age and level of activity of the patient. Expert advice is that each of these factors are equally as important as lesion size when deciding to proceed with one surgery over another.

9.   Comparator

The comparator is MF surgery on its own, which is listed in the MBS system under items 49561, 49562 and 49563. Considering that other courses of treatment for knee focal cartilage injuries, such as ACI and MACI, are rarely used (nor reimbursed) in Australia, the Commentary considered that MF surgery alone is deemed an appropriate comparator.

10.   Comparative safety

The key features of the included evidence base are described in Table 3.

Table 3   Key features of the included evidence comparing microfracture with microfracture plus BST-CarGel

Trial/Study	N	Design/ duration	Risk of bias	Patient population	Key outcome(s)	Result used in economic model
Stanish et al. 2013	80	R, MC, SB* 12 mths	*Repair quantity (low) Repair quality (some concerns)*	Patients 18 to 55 years old with a single, symptomatic focal lesion (up to 10 cm^2) located on the femoral condyle and classified as grade 3 or 4 (on Outerbridge scale) with moderate knee pain (>4 cm on a 10 cm VAS scale)	Repair tissue quantity and quality	Repair tissue quantity only
Shive et al. 2015†	67‡	NRa, MC, SB* 5 years	*Serious risk for both quantity and quality*	Patients from Stanish et al (2013) study who consented to participate in a 5-year follow-up study	Repair tissue quantity and quality	No
Méthot et al. 2016†§	*38*	*NRa, MC, SB* 13 mths*	*Serious risk for all ICRS scores*	*Patients from Stanish et al. (2013) who consented to participate in a 2nd look arthroscopy and biopsy study*	*ICRS macroscopic scoring. Structural parameters as assessed by histology*	*No*
Sofu et al. 2019‖	*46*	*CS, Retro, Con, 24 mths (mean)*	*NA*	*Patients with a symptomatic single focal defect of the either medial or lateral femoral condyle classified as an Outerbridge grade 3 or 4 lesion. Mean lesion size of 3.3 ± 0.7 cm^2*	*VAS, Lysholm knee score, Tegner activity scale, quality of repair tissue*	*No*

Notes
*Only the people carrying out the analyses of primary endpoints were blinded. Investigators and patients were not blinded. It should be noted in the study by Méthot et al. 2016 that whilst the histological analyses were conducted by blinded assessors the assessors of the macroscopic ICRS score were not blinded.
†Extension studies of subsets of patients from Stanish et al (2013) trial
‡ Whilst 67 patients agreed to participate in this follow-up study, the number of patients with data available varied from year to year with data available for 60 patients at year 5.
§Data from this study was included by the Applicant but the study was not included in their table of key features of included evidence (Table 20 of ADAR, page 53 and Table 21 of Commentary, page 63)
‖ This study was identified by the Applicant but not used as evidence in their submission as it had the wrong comparator. The Commentary decided to include the single arm of this study as a case series for safety and thus have included its details in the table of key features of the evidence. It is discussed in Section B7 of the Commentary.
Abbreviations: CS=case series; Con = consecutive enrolment; ICRS: Internal Cartilage Repair Society; MC=multi-centre; NA: not applicable; NRa=non-randomised; QoL=quality of life; R=randomised; Retro = retrospective; SB=single blind; VAS: Visual Analogue Scale
Source: Table 3, pxvii of the Commentary

The Commentary stated that the sponsor of the pivotal randomised controlled trial (RCT) was the company who owned BST-CarGel at the time. Conflicts of interest are noted with all three studies relating to associations with the sponsor.

The Commentary stated that the patients in the studies have lesion sizes covering both populations stipulated in the PICO, although with an average lesion size closer to population one, and results are not separated for lesion size. It is uncertain whether some of the patients may have had damage to the subchondral endplate, an exclusion criterion specified in the PICO.

Results for all safety outcomes as reported by the Commentary are presented in Table 4.

The Commentary stated that at 12 months follow-up, the number of adverse events (any type) reported for BST-CarGel plus microfracture was similar to that reported for microfracture alone. These events were generally mild to moderate and included arthralgia, procedural pain and nausea. No deaths or discontinuations due to an adverse event occurred. Device-related adverse events (those relating to BST-CarGel) were reported in 9/41 (22 %) of patients. Whilst the study did not specifically report what these were, according to the definition provided in the clinical study report (CSR) they were either shellfish hypersensitivity or chronic inflammation within the knee. There is uncertainty regarding the serious adverse events as only the number of these were reported, not what they actually were (5/41 patients [9.8%] for BST-CarGel plus microfracture compared with 1/39 [2.6%] for microfracture alone). The only other detail provided regarding these serious adverse events was that 4 out the 5 reported for BST-CarGel were procedure related.

The Commentary stated that as for the 12-month follow-up study, reporting for the 5-year follow-up was also poor. Again, they reported the number of adverse events and whether they were device or procedure related or serious, but not what they were. It is reported that most were considered mild to moderate in severity and that the most frequently observed adverse event in both the BST-CarGel plus microfracture and microfracture alone groups was knee pain. No deaths or discontinuations due to adverse events occurred. Adverse events over five years decreased from the 12-month follow-up for both BST-CarGel plus microfracture and microfracture alone. Owing to the serious risk of bias associated with the 5-year follow-up study there is uncertainty regarding the adverse event numbers and no comparisons were made between BST-CarGel plus microfracture and microfracture alone.

Table 4   Balance of clinical benefits and harms of BST-CarGel plus microfracture, relative to microfracture alone, and as measured by the critical patient-relevant outcomes in the key studies

No of studies (k=)	Study Design/s	Risk of bias	Consistency of findings	Applicability (including indirectness)	Imprecision	Other considerations	Intervention	Control	Relative (95% CI)	Quality[a]
							No of patients[b]		Effect	
Patient-relevant critical effectiveness outcome (eg from PICO in PICO Confirmation) - degree of lesion fill as assessed by MRI (scale: 0-100%) measured at 12 months follow-up										
Degree of lesion fill (k = 1)	RCT	Not serious	NA	Serious[C]	Serious[D]	No	41	37	MD (95% CI) 7.59 (1.95, 13.23) p = 0.011	⊕⊕⊙⊙
Patient-relevant critical effectiveness outcome (eg from PICO in PICO Confirmation) - T2 relaxation time (ms) as assessed by MRI / measured at 12 months follow-up										
T2 relaxation time (k = 1)	RCT	Some concerns	NA	Serious[C]	Serious[D]	No	39	33	MD (95% CI) -14.58 (-27.59, -1.57) p = 0.011	⊕⊕⊙⊙
Patient-relevant critical effectiveness outcome (eg from PICO in PICO Confirmation) – Structural success (% fill > 70 %) as assessed by MRI / measured at 12 months follow-up										
Structural success (k = 1)	RCT	Not serious	NA	Serious[C]	Serious[E]		41	37	RR (95% CI) 1.20 (1.02, 1.42), P = 0.03 RD (95% CI) 0.16 (0.03, 0.30), NNT = 7	⊕⊕⊙⊙
Patient-relevant critical effectiveness outcome (eg from PICO in PICO Confirmation) – WOMAC (change from baseline) / measured at 12 months follow-up										
WOMAC (k = 1)	RCT	Some concerns, Not marked down	NA	Serious[F]	Very serious[G]		40	37[b]	MD (95% CI) Pain: 0.75(-2.54, 4.04) Stiffness: 0.59 (-1.33, 2.51) Function: 4.63 (-7.35, 16.61)	⊕⊙⊙⊙
Patient-relevant critical effectiveness outcome (eg from PICO in PICO Confirmation) – SF-36 (change from baseline) / measured at 12 months follow-up										
SF-36 (k = 1)	RCT	Serious	NA	Some concerns[H]	Very serious[G]		36	34	MD (95% CI) Physical component: -1.74 (-5.93, 2.45) p = 0.412	⊕⊙⊙⊙

Quality assessment							No of patients[b]		Effect	Quality[a]
No of studies (k=)	Study Design/s	Risk of bias	Consistency of findings	Applicability (including indirectness)	Imprecision	Other considerations	Intervention	Control	Relative (95% CI)	
									Mental component: 2.70 (-1.65, 7.05) p = 0.229	
Patient-relevant critical effectiveness outcome (eg from PICO in PICO Confirmation) - degree of lesion fill as assessed by MRI (scale: 0-100%) measured at 5-year follow-up										
Degree of lesion fill (k = 1)	Non-randomised comparative	Serious	NA	Serious[C]	Serious[D]		33	26	MD (95% CI) 6.80 (0.82, 12.78) p = 0.017	⊕⊙⊙⊙
Patient-relevant critical effectiveness outcome (eg from PICO in PICO Confirmation) – T2 relaxation time (ms) as assessed by MRI / measured at 5-year follow-up										
T2 relaxation time (k = 1)	Non-randomised comparative	Serious	NA	Serious[C]	Serious[D]		29	22	-14.70 (-31.30, 1.90) p = 0.026)	⊕⊙⊙⊙
Patient-relevant critical effectiveness outcome (eg from PICO in PICO Confirmation) – WOMAC (change from baseline) / measured at 5-year follow-up										
WOMAC (k = 1)	Non-randomised comparative	Serious	NA	Serious[F]	Very serious[G]		33	26	MD (95% CI) Pain: 1.62(-2.11, 5.35) Stiffness: 0.59 (-1.33, 2.51) Function: 5.02 (-6.60, 16.64)	⊕⊙⊙⊙
Patient-relevant critical effectiveness outcome (eg from PICO in PICO Confirmation) – SF-36 (change from baseline) / measured at 5-year follow-up										
SF-36 (k = 1)	Non-randomised comparative	Serious	NA	Some concerns[H]	Very serious[G]		34	26	MD (95% CI) Physical component: -1.07 (-5.31, 3.17) Mental component: 2.89 (-1.42, 7.20)	⊕⊙⊙⊙
Patient-relevant critical safety outcome (eg from PICO in PICO Confirmation) – any adverse events / measured at 12 months follow-up										
Any adverse events (k=1)	RCT	Some concerns Not enough to mark down	NA	Not serious	Some concerns[I]	0	41	39	RR (95% CI) 1.06 (0.95, 1.17), p = 0.29 RD (95% CI)	⊕⊕⊕⊕

No of studies (k=)	Study Design/s	Risk of bias	Consistency of findings	Applicability (including indirectness)	Imprecision	Other considerations	Intervention	Control	Relative (95% CI)	Quality[a]
				Quality assessment			**No of patients[b]** Intervention / Control		**Effect** Relative (95% CI)	
									0.05 (-0.04,0.15) -	
**Patient-relevant critical safety outcome (eg from PICO in PICO Confirmation) - serious adverse events/ measured at 12 months follow-up**										
Serious adverse events (k =1)	RCT	Some concerns Not enough to mark down	NA	Not serious	Some concerns[l]	0	41	39	RR (95% CI) 4.76 (0.58, 38.91) p = 0.15 RD (95% CI) 0.10 (-0.02, 0.21)	⊕⊕⊕⊕ Type of SAE not known, said to be procedure related, this likely to be done via different approach majority of times i.e. arthroscopy not arthrotomy
**Patient-relevant critical safety outcome (eg from PICO in PICO Confirmation) – procedure-related adverse events / measured at 12 months follow-up**										
Procedure-related adverse events	RCT	Some concerns Not enough to mark down	NA	Not serious	Some concerns[l]	0	41	39	RR (95% CI) 1.20 (0.99, 1.46), p = 0.06	⊕⊕⊕⊕
**Patient-relevant critical safety outcome (eg from PICO Confirmation) - adverse events / measured at 5-year follow-up**										
Any adverse events (k = 1)	Non-randomised comparative	Serious	NA	Not serious	Some concerns[l]	0	33	26	NR	⊕⊕⊕⊙ Most events occur in first 12 months
**Patient-relevant critical safety outcome (eg from PICO in PICO Confirmation) - serious adverse events / measured at 5-year follow-up**										
Serious adverse events (k = 1)	Non-randomised comparative	Serious	NA	Not serious	Some concerns[l]	0	33	26	NR	⊕⊕⊕⊙

Quality assessment							No of patients[b]		Effect	Quality[a]
No of studies (k=)	Study Design/s	Risk of bias	Consistency of findings	Applicability (including indirectness)	Imprecision	Other considerations	Intervention	Control	Relative (95% CI)	
Patient-relevant critical safety outcome (eg from PICO in PICO Confirmation) – procedure-related adverse events / measured at 5-year follow-up										
Procedure-related adverse events (k = 1)	Non-randomised comparative	Serious	NA	Not serious	Some concerns[I]	0	33	26	NR	⊕⊕⊕⊙

[a] GRADE Working Group grades of evidence (Guyatt et al., 2013); [b] When our patient numbers differ from what is reported in the ADARs Table we have written the number we believe is correct in red, [C] Evidence for Pop 1 and 2 combined, surrogate outcome, unsure of validity, [D] Wide CI, small sample size, only 1 study, no defined clinically relevant effect size, [E] One study, small total number patients, [F] Evidence for Pop 1 and 2 combined, unsure of validity for articular cartilage injuries, [G] Concern in wide CIs, study not powered to detect a difference, [H] Pop 1 and 2 combined, [I] One study, small number of patients

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

Abbreviations: MD: mean difference; MRI: magnetic resonance imaging; ms: milliseconds; NNT: number needed to treat; NR: not reported; PICO: patients, intervention, comparator, outcomes;

SF-36: short form 36 health survey; RD: risk difference; RR: relative risk; WOMAC: Western Ontario and McMaster Universities Arthritis Index

Source: Table 4, pp xxii-xxv of the Commentary

11.   Comparative effectiveness

Results for all effectiveness outcomes as reported by the Commentary are presented in Table 4.

Structural outcomes
The ADAR's key primary effectiveness outcomes are structural outcomes including degree of lesion fill (%), repair cartilage T2 relaxation time and structural success (% fill > 70%).

The Commentary considered there was uncertainty regarding the relevance of the main effectiveness outcomes, lesion quantity (percent lesion fill) and lesion quality (T2 relaxation time), which are the basis for the Applicant's claim of superior effectiveness. Specifically, it is unknown whether differences in these outcomes translate into differences in pain and function experienced by the patient and if they do, what is the minimum difference required in each for these effects to be realised.

Statistically significant better results for all these structural parameters were found for BST-CarGel plus microfracture compared with microfracture alone at 12 months. The Commentary stated that significantly better results were also observed for BST-CarGel plus microfracture for degree of lesion fill (%) and repair cartilage T2 relaxation time at 5 years. Structural success was not reported at this follow-up. The Commentary stated that there were several reasons why these results should be interpreted with caution:

- It is unknown whether these parameters, measured by magnetic resonance imaging (MRI), are valid surrogates for patient-relevant outcomes and perceived outcomes of reduced knee pain and increased functionality.
- It is unclear what the minimum clinically important differences required for each of these parameters for a patient to perceive a difference in knee pain or functionality is.
- Excluding structural success, there are wide confidence intervals for both degree of lesion fill (%) and repair cartilage T2 relaxation time resulting in a lack of certainty regarding the differences observed.
- The findings were derived from one RCT.

In the pre-ESC response, the applicant stated that percent lesion fill provides an objective measure of effectiveness for which a link to patient relevant outcomes exist. Furthermore, the applicant considered that a moderate correlation between MRI parameters and clinical outcomes has been reported (Blackman 2013[5]; de Windt 2013[6]). The meta-analysis by Blackman (2013) showed defect fill to have a moderate to good correlation (r: [95% confidence interval [CI]:0.693: [0.358, 0.870]) with clinical outcomes.

The ADAR advised that the threshold of < 70% for treatment failure is broadly based on the categorisation of cartilage lesion fill as per Mithoefer (2009)[7] of good (67–100% fill), moderate (34–66% fill) and poor (0–33% fill). Given the correlation between lesion fill and clinical outcome as discussed above, treatment success is considered an important link to clinically relevant outcomes for patients undergoing lesion repair.

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[5] Blackman AJ, Smith MV, Flanigan DC, et al. Correlation between magnetic resonance imaging and clinical outcomes after cartilage repair surgery in the knee: a systematic review and meta-analysis. Am J Sports Med. 2013;41(6):1426-34.
[6] De Windt T, Welsch G, Brittberg M, et al. Is magnetic resonance imaging reliable in predicting clinical outcome after articular cartilage repair of the knee? A systematic review and meta-analysis. Am J Sports Med. 2013;41(7):1695-702.
[7] Mithoefer, K., Mcadams, T., Williams, R. J., Kreuz, P. C. & Mandelbaum, B. R. 2009. Clinical efficacy of the microfracture technique for articular cartilage repair in the knee: an evidence-based systematic analysis. Am J Sports Med, 37, 2053-63.

Patient-relevant outcomes

The Commentary considered there is also uncertainty regarding the patient reported Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) outcome, which is a tool developed and validated for people with osteoarthritis of the hip or knee. Its applicability to the proposed MBS population including people with articular cartilage damage of the knee is unknown.

The Commentary also highlighted concerns with bias for both the WOMAC and the SF-36 outcomes as these are patient reported and patients knew what treatment they received. There are also concerns with bias in the reporting of adverse events as these were recorded by investigators who knew what treatment the patients had received. There are serious bias issues with all outcomes from both follow-up studies including the histology outcomes assessed at 13 months and the structural and patient outcomes from the 5-year follow-up study. These serious bias issues are due to the patients from the RCT, who knew what treatment they received, choosing whether to participate in these follow-up studies.

The Commentary stated that the assessment of clinical effectiveness using patient relevant outcomes (WOMAC and SF-36) failed to detect a statistically significant difference between intervention and comparator groups; however, these studies were not powered to detect differences in these outcomes and therefore conclusions on relative effectiveness with respect to these outcomes are uncertain.

Clinical claim

The ADAR's clinical claim for BST-CarGel plus microfracture is non-inferior safety and superior effectiveness compared with microfracture alone.

The Commentary considered:

- the clinical claim of non-inferior safety is justified for both the short term (12-month follow-up) and longer term (5-year follow-up).
- for the structural outcomes, the clinical claim of superior effectiveness is justified in the short term (12-month follow-up) but not the longer term (5-year follow up). This is because of serious selection bias in the 5-year follow-up study resulting in uncertainty in the data. It should be taken into consideration; however, that the claim of superior effectiveness at 12 months is based on structural outcomes measured by MRI. The evidence regarding whether these MRI structural outcomes correspond to improved patient wellbeing (decreased pain, increased function) is conflicting. although it was the opinion of a clinical expert that per cent fill is a reasonable measure of success with a quantity of around 70 to 80 per cent required for a good outcome (Personal communication, orthopaedic surgeon).
- for patient relevant outcomes, the claim of superior effectiveness may not be supported as results for these outcomes were not statistically significant. The caveat to this finding is that the primary research was not powered to detect a difference in these outcomes, therefore the interpretation is subject to uncertainty.

In the pre-ESC response, the applicant highlighted that improvement in cartilage quality and quantity is expected to result in improved outcomes over time (Case 2016[8]). The applicant considered on the basis of superior structural outcomes observed with CARGEL+MF relative to MF alone at 12 months, coupled with the correlation between structural outcomes and clinical outcomes, it may be expected that CARGEL+MF will provide superior clinical outcomes relative to MF alone over the longer term.

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[8] Case JM, Scopp JM. Treatment of Articular Cartilage Defects of the Knee with Microfracture and Enhanced Microfracture Techniques. Sports Med Arthrosc Rev 2016;24:63–68)

Translation issues

The Commentary considered that issues have arisen due to the translation of structural outcome data collected at 12 months into a measure of clinical success (alleviation of knee pain) that is maintained over 20 years (base case). These are:

- the translation of a surrogate outcome into a measure of clinical success despite WOMAC and SF-36 data having been collected in the clinical trial (and showing no difference)
- the assumption that knee pain is the primary contributor to quality of life in patients suffering with an articular cartilage defect and the application of utilities accordingly
- the extrapolation (in the base case) of the incremental difference in patients achieving clinical success (itself a derived estimate) at 12-months over 20 years without considering the longevity of the intervention (is cartilage repair surgery curative or is regression expected), nor whether failed cases may require reintervention (Table 5).

Table 5   Summary of results of pre-modelling studies and their uses in the economic evaluation

Pre-modelling study	Results	Use in Section D	Cross-Ref	Use in Section D.6	Cross-Ref
Applicability pre-modelling studies					
None conducted	*At a high level, the population is broadly representative of patient who will receive MBS-funded services*	*NA*		*NA*	
Extrapolation pre-modelling studies					
None conducted	*Treatment effect is assumed to be maintained over 20 years. This may not be appropriate given the assumptions made in the base case regrading disease/patient management pathways.*	*NA*		*NA*	
Transformation pre-modelling studies					
Surrogate to measure of clinical success	Correlation between lesion fill and clinical outcome: r = 0.69 (95% CI = [0.36, 0.87]), which is rescaled by the Applicant. Rescaled correlation coefficient used to derive the proportion of patients with clinical success. *The equation used to rescale the correlation coefficient could not be verified. Use of the equation appears to unnecessarily inflate correlation between structural and clinical outcomes. This favours the intervention.*	Yes. Correlation coefficient informs the derivation of the percent of patients achieving clinical success	Section D.4	Upper and lower bounds of the 95% CI of the correlation coefficient are used.	Section D.6
Assignment of utilities to health states	No knee pain: 0.92 Knee pain: 0.8	Yes. Utility values are assigned to the health states	Section D.4	Results from pre-modelling study not used. Utility tested via ± 25% change in the difference in utility.	Section D.6

Source: Table 45, pp116-117 of the Commentary

12. Economic evaluation

The ADAR assessed the cost effectiveness of BST-CarGel use relative to microfracture alone by conducting both a 12-month trial-based cost effectiveness analysis (with two different outcome measures) and a 20-year, modelled cost utility analysis (Table 6).

Table 6   Summary of the economic evaluation

Perspective	Australian healthcare system
Comparator	Microfracture alone
Type of economic evaluation	Trial-based CEA and modelled CUA
Sources of evidence	RCT evidence (Stanish et al. 2013)
Time horizon	12 months (CEA) 20 years (CUA) (base case)
Outcomes	Structural success, defined as lesion fill of >70% (CEA outcome) Clinical success (assumed to be the relief of knee pain) Quality-adjusted life years (QALYs) (CUA outcome)
Methods used to generate results	Trial-based (CEA) State-transition cohort (Markov) model (CUA)
Health states (CUA only)	• Initial treatment • 1L success – clinical success (no knee pain) after initial treatment • 1L failure – clinical failure (ongoing knee pain) after initial treatment • 2L success – clinical success (no knee pain) after subsequent treatment † ‡ • 2L failure – clinical success (ongoing knee pain) after subsequent treatment † ‡ • Dead
Cycle length (CUA only)	1 year
Discount rate	5 % (base case)
Software packages used	Microsoft Excel

Abbreviations: CEA = cost effectiveness analysis; CUA = cost utility analysis, QALY = quality-adjusted life year; RCT = randomised controlled trial
Notes: 1L and 2L differentiate between health states entered following either the initial or secondary surgery, respectively
† = these health states are only ever occupied in sensitivity analyses (i.e. not in the base case); ‡ = where included (sensitivity analysis only), subsequent treatments are possible only once per patient therefore, once in the 2L success or failure state, a patient can only remain in the respective state, or transition to the dead (absorbing) state.
Source: adapted from Table 45 (p.92) of the ADAR document

The key structural assumptions of the ADAR's model are:
- Structural outcomes are correlated with clinical outcomes
- Knee pain is a primary contributor to quality of life in focal cartilage defects
- Successful treatment relieves patient symptoms (i.e. knee pain)
- No risk of subsequent treatment (in the base case)
- Treatment success/failure is sustained for the duration of the model.

The Commentary sought expert advice, which suggested that microfracture (alone) is not considered a long-term cure and often, patients need to go on to other procedures later in life (Personal communication, orthopaedic surgeon). Based on the advice received, the Commentary considered it was unlikely that there are no subsequent surgical treatments, nor any regression, over a 20-year period.

In addition, the Commentary considered that a binary measure of clinical success (which essentially represents the relief, or not, of knee pain) was derived via application of a correlation coefficient to the surrogate outcome (structural success). The Commentary considered this step is problematic and introduces a great degree of uncertainty into the model. In the pre-ESC response, the applicant acknowledged this uncertainty; however, considered it was not an unreasonable assumption that 69.3% of the patients who benefit from CARGEL on structural outcomes go on to benefit in terms of clinical and quality of life outcomes.

The results of a stepped analysis of the economic evaluation are given in Table 7. The Commentary revised the ADAR's base case model in red italics below, making small technical changes: updating the annual discount formula, background mortality probability, cost of surgical assistance, transition to death in the first cycle and the comparator health state cost (use of discounted value).

Despite resolving these small technical issues, the Commentary considered these did not reduce the uncertainty in the incremental cost effectiveness ratio (ICER) value. Furthermore, the Commentary considered no updates could readily be made to improve our confidence in the estimated ICER value – the uncertainty rests largely on the poor-quality clinical data of which, informative results are limited to 12-month structural outcomes. Both the original and updated base case results should be interpreted with caution.

Table 7   Results of the stepped analysis

Step	Description	Costs included	Effectiveness	Duration	Incr. cost	Incr. effect	ICER
1	Trial-based *Result of the CEA*	Procedure only	Proportion of patients with lesion fill >70%	1 year	$redacted	16.5%	$redacted per additional patient with lesion fill response
2	Trial-based with application of correlation coefficient	Procedure only	Proportion of patients with clinical success[a]	1 year	$redacted	11.4%	$redacted per additional patient with successful clinical outcome
3	Extrapolation of costs and outcomes	Procedure and health states	QALYs *(derived from literature review)*	5 years	$5,762 *$5,843*	0.053 *0.054*	$108,236 per QALY gained *$109,017 per QALY gained*
4				10 years	$5,352 *$5,650*	0.099 *0.10*	$53,829 per QALY gained *$56,135 per QALY gained*
5	*Result of the base case CUA*			20 years	$4,369 *$5,385*	0.162 *0.166*	$26,981 per QALY gained *$32,541 per QALY gained*

Abbreviations: CEA = cost effectiveness analysis; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year
Source: Adapted by Commentary from Table 61 (p.110) of the ADAR report.
Note Commentary revised the ADARs base case model, updating the annual discount formula, background mortality probability, cost of surgical assistance, transition to death in the first cycle and the comparator health state cost (use of discounted value).
a Based on lesion fill using Blackman 2013
Italicised represents comments added in during ESC

The Commentary stated that model outcomes were highly sensitive to both the applied correlation between MRI and clinical outcomes and the time horizon selected, with greatest volatility being displayed at the lower end of the tested ranges and in the direction of increasing the ICER (Figure 2).

Redacted - Figure 2   **Tornado diagram**

The Commentary performed additional multivariate sensitivity analyses within the bounds of the ADAR's model structure, which demonstrated that the model is volatile when annual regression and/or reintervention rates are manipulated to force the reintervention rate at 20 years in the microfracture arm to ≈ 56% (Table 8). The Commentary stated that manipulation of model parameters to fabricate situations which may better reflect expected long-term outcomes in the microfracture arm suggest the misalignment between the extrapolated and expected patient pathways after microfracture are of concern. Overall, the Commentary had little confidence in results of the economic evaluation.

Table 8   Multivariate analyses on regression and reintervention rates performed for the Commentary and for the pre MSAC response (in blue)

Scenario				Incr. cost	Incr. QALYs	ICER
% regress	% retreat	Retreat procedure	Retreat success			
Treatment failure/reintervention at 20 years (goal seek)						
Commentary (analyses based on CEA by Elvidge 2016)						
1 5%	*11.45%*	50% MF and 50% TKR †	0.85 ‡	*$redacted*	*redacted*	*$redacted*
2 *7.88%*	*7.88%*			*$redacted*	*redacted*	*$redacted*
3 *22.5%*	5%			*$redacted*	*redacted*	*$redacted*
Pre-MSAC response (analyses based on Knutsen 2016) conducted by the Applicant						
4 5.0%	6.0%	50% MF and 50% TKR †	0.85 ‡	$redacted	0.0790	$redacted
5 5.6%	5.6%			$redacted	0.0774	$redacted
6 6.8%	5%			$redacted	0.0738	$redacted

Abbreviations: *BC = base case;* ICER = incremental cost effectiveness ratio; MF = microfracture; QALYs = quality adjusted life years; TKR = total knee replacement
Notes: † = as per Applicant's assumption stated on p.103 of the ADAR report; ‡ = as per the Applicant's assumed rate. This was unaltered.
Source: Table 9, p xxxii of the Commentary and Table 1, p6 of pre-MSAC response

In the pre-ESC response, the applicant highlighted that the trial-based cost-effectiveness analysis (ICER = $**redacted** per additional patient with lesion fill response) supports value for money for CARGEL+MF vs. MF.

In the pre-MAC response, the applicant performed additional multivariate sensitivity analyses using data from Knutson (2016)[9], which was a randomised multicentre trial comparing autologous chondrocyte implantation (ACI) to MF, reporting treatment failure rates at 15 years of 17/40 patients (42.5%) for ACI and 13/40 (32.5%) for MF. Using this data and assuming exponential use of subsequent treatments, the reintervention rate was estimated at 41% for 20 years for MF[10] (rather than 56% at 20 years from Elvidge (2016[11]), which the applicant considered was not reasonable estimate due to the author's methodology of estimating the failure rate of MF with extrapolating parametric survival curves over 20 years (from 5 years clinical data); and the extrapolations deviate significantly from each other over 20 years (CCI=34%; MF=56%), despite similar rates of failure at 5 years (end of follow-up), approximately 15% (Figure 3). In addition, the applicant noted the wide range of retreatment

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[9] Knutsen G, Drogset JO, Engebretsen L, Grøntvedt T, Ludvigsen TC, Løken S, Solheim E, Strand T, Johansen O. 2016. A randomized multicenter trial comparing autologous chondrocyte implantation with microfracture: long-term follow-up at 14 to 15 years. JBJS Aug 17;98(16):1332-9.
[10] $1-(1-32.5\%)20/15$
[11] Elvidge, J., Bullement, A. & Hatswell, A. J. 2016. Cost Effectiveness of Characterised Chondrocyte Implantation for Treatment of Cartilage Defects of the Knee in the UK. Pharmacoeconomics, 34, 1145-1159.

rates with heterogenity in the definition of treatment failure (40% over 10 years [Weber 2018[12]], 20% over 5 years [Vanlauwe 2011[13]], 70% at 15 years [Solheim 2020[14]]).
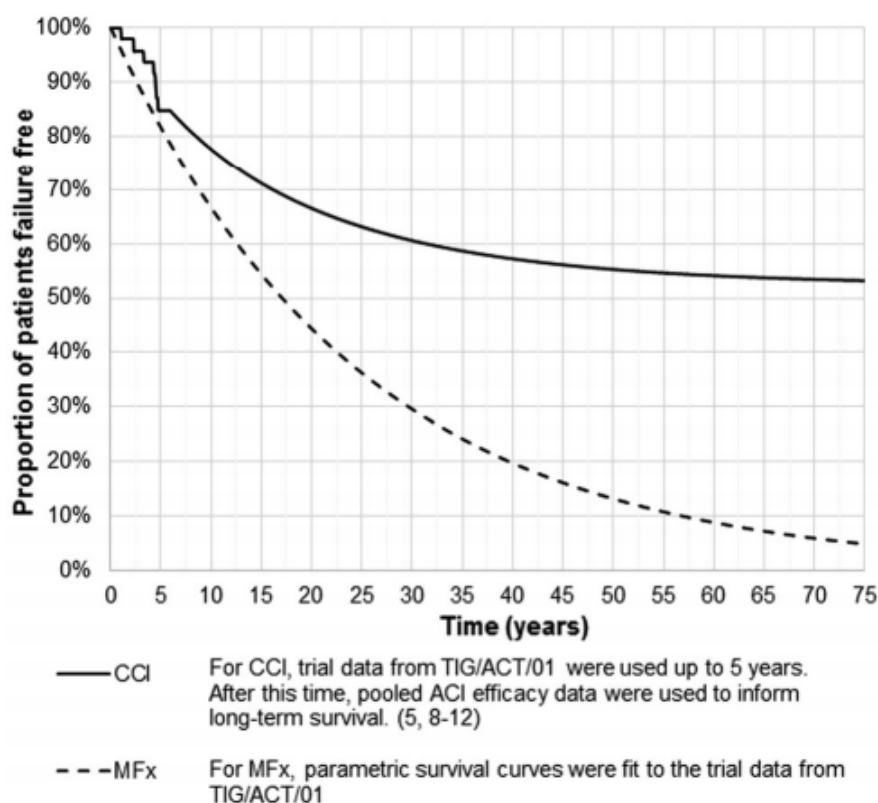

Figure 3   Estimation of long-term treatment failure in Elvidge (2016)
Source: Figure 1, p6 of pre-MSAC response
Reprinted by permission from Springer Nature: Springer Nature PHARMACOECONOMICS, 34, 1145-1159 (Cost Effectiveness of Characterised Chondrocyte Implantation for Treatment of Cartilage Defects of the Knee in the UK., Elvidge, J., Bullement, A. & Hatswell, A.J.), COPYRIGHT (2016), advance online publication, 18 June 2016 (https://doi.org/10.1007/s40273-016-0423-y. Pharmacoeconomics.)

13.   Financial/budgetary impacts

A market share approach was used by the ADAR to estimate the budgetary impact of continued BST-CarGel use via the MBS and Prostheses List. BST-CarGel has been listed on the Prostheses List since August 2015 (Billing Code: SL072); recent utilisation data was thus available.

The Commentary stated whilst two distinct patient populations (differentiated by lesion size) were defined in the ratified PICO, a single combined population is considered in the financial analysis because confidential Prostheses List sales data (provided by the Applicant) did not distinguish between the two populations. The Commentary considered the use of a single combined population is appropriate for the financial analysis. The Commentary cited expert advice, which indicated that most cartilage defects will be 4 cm^2 or less and that in the rare

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[12] Weber AE, Locker PH, Mayer EN, Cvetanovich GL, Tilton AK, Erickson BJ, Yanke AB, Cole BJ. 2018. Clinical outcomes after microfracture of the knee: midterm follow-up. Orthopaedic journal of sports medicine Feb 6;6(2):2325967117753572.

[13] Vanlauwe J, Saris DB, Victor J, Almqvist KF, Bellemans J, Luyten FP, TIG/ACT/01/2000&EXT Study Group. 2011. Five-year outcome of characterized chondrocyte implantation versus microfracture for symptomatic cartilage defects of the knee: early treatment matters. The American journal of sports medicine Dec;39(12):2566-74.

[14] Solheim E, Hegna J, Inderhaug E. 2020. Long-term survival after microfracture and mosaicplasty for knee articular cartilage repair: a comparative study between two treatments cohorts. Cartilage Jan;11(1):71-6.

cases where the defects are larger than this, approaches other than microfracture would likely be selected (Personal communication, orthopaedic surgeon).

The financial implications to the MBS resulting from the continued listing of BST-CarGel on the MBS and Prostheses List over the next five years (beginning 2021) are summarised in Table 9. All services contributing to the financial estimates are in-hospital services. The Commentary updated the financial estimates to include the additional MBS services required in conjunction with the intervention and comparator (anaesthesia and surgical assistance) [displayed in red italic font in Table 9]. The Commentary considered that the net cost impact of continued BST-CarGel reimbursement to the MBS is minimal, and that uncertainty is not a major issue.

Table 9   Net cost impact to the MBS of continued BST-CarGel reimbursement

Row	Parameter	Year 1	Year 2	Year 3	Year 4	Year 5	Source
A	Patient (service) number	Redacted	Redacted	Redacted	Redacted	Redacted	Table 89 of Commentary
	Scenario: continuing funding for BST-CarGel						
B	Cost of procedure	$redacted	$redacted	$redacted	$redacted	$redacted	Table 90 of Commentary
C	Cost of associated services	*$43,641*	*$44,347*	*$45,044*	*$45,733*	*$46,410*	Table 93 of Commentary
D	Total cost	$redacted *$redacted*	$redacted *$redacted*	$redacted *$redacted*	$redacted *$redacted*	$redacted *$redacted*	B + C
	Scenario: ceasing to fund BST-CarGel						
E	Cost of procedure †	$redacted	$redacted	$redacted	$redacted	$redacted	
F	Cost of associated services	*$38,514*	*$39,137*	*$39,752*	*$40,360*	*$40,958*	
G	Total cost	$redacted *$redacted*	$redacted *$redacted*	$redacted *$redacted*	$redacted *$redacted*	$redacted *$redacted*	
	-						
	Net cost impact (Applicant estimate)	$0	$0	$0	$0	$0	B - E
	Net cost impact of continued BST-CarGel reimbursement	*$5,127*	*$5,210*	*$5,292*	*$5,373*	*$5,453*	D - G

Notes: † = assuming a one-to-one substitution with microfracture alone
Source: Table 10, p xxxiv of the Commentary

In the pre-MSAC response, the applicant indicated that since the PL listing of a competitor product on 1 July 2019, the sales of CARGEL has **redacted**. This **redacted** in CARGEL sales, which continues to **redacted**, would also be linked with a **redacted** in the MBS costs associated with the use of CARGEL.

Thus, the applicant considered that the continued listing of CARGEL on the PL will have no additional budget implications yet will allow ongoing access for patients to a superior treatment option.

14.   Key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
Population	Evidence base is not analysed separately by lesion size (2 cm² threshold), as per PICO subpopulations- thus the clinical effectiveness of BST-Cargel for each subpopulation could not be determined.
Safety	To note uncertainty due to the RCT using arthrotomy, whereas clinical practice generally uses arthroscopy
Structural outcomes as surrogates for patient-relevant outcomes	There was high uncertainty whether the structural outcomes on MRI, which the clinical claim of superior effectiveness relied upon, are valid surrogates and correlate well enough with patient-relevant outcomes (e.g. WOMAC or SF-36). Furthermore, the pivotal trial failed to detect a difference in these patient relevant outcomes (albeit was not powered to do so).
	In addition, there was also uncertainty with the relevance of WOMAC outcome, as it's validated in a different condition and population.
	To note Commentary that while ICRS score can be the same and "structural success" achieved, surgery may still be required
Evidence base- comparative effectiveness – uncertain clinical benefit	Short term structural outcomes; relies upon one RCT up to 12 months with a potential conflict of interest.
	Longer term; data from the 5-year follow-up study is uncertain primarily from a high loss to follow-up.
Overall, little confidence in the health economic evaluation	There are many uncertainties in health economic outcomes, mainly due to uncertain clinical benefit, uncertainty about subsequent treatments and the extrapolation of benefit over 20 years.
Financial impact- continued listing	Net cost impact of continued CARGEL reimbursement to the MBS is minimal.
	MSAC may wish to consider if uncertainties were sufficient to discuss alternatives to not continued listing/de-listing.
Billing Item number	MSAC to consider need for a separate MBS item number or amendment of the current number. The proposed ADAR fee is the same as MBS 49561
Consumer feedback	To note absence of consumer / support group feedback

ESC discussion

ESC noted that this application is from the Prostheses List Advisory Committee (PLAC) requesting a health technology assessment (HTA) from MSAC for BST-CARGEL™ to determine the clinical- and cost-effectiveness of this product, and to clarify the appropriateness of MBS item 49561. ESC also noted that BST-CARGEL has been reimbursed via the MBS and the Prostheses List (PL) since August 2015, with the PL listing not limited by joint location. ESC recalled that PASC recommended that the HTA be restricted to the knee, given most evidence relates to this.

ESC noted that the populations were not analysed separately (or disaggregated) by lesion size (2 cm² threshold). Thus, whether the clinical effectiveness of BST-Cargel differs for each subpopulation could not be determined. However, ESC also agreed with the applicant in the pre-ESC response, that this might be acceptable because the comparator is microfracture (MF) for both subpopulations in Australia. ESC also recalled PASC advice, which noted 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.

ESC also noted that there are no restrictions on age or body mass index (BMI) in the proposed population. ESC recalled PASC advice, which considered that there is no reason to impose an upper age limit, but acknowledged that MSAC may choose to have an age limit in the MBS item descriptor. ESC noted that the applicant is committed to working with the Department to finalise a suitable item descriptor dependent on the preferred approach (new MBS item code, as suggested by PASC [Table 2], amended MBS item code, or unchanged MBS item code), and that the proposed fee for this service is identical to that of existing MBS item 49561. ESC also noted that these issues have not been resolved yet. In addition, ESC noted that the word 'focal' was used in the application title but not in the MBS item descriptor.

ESC considered the clinical management algorithm presented in the ADAR, noting its consistency with the ratified PICO. ESC noted the Commentary consulted an independent clinical expert who stated that MF surgery is appropriate for the treatment of knee cartilage lesions of up to 5cm^2. ESC also noted that age and level of activity of the patient are important considerations, which are not included in the algorithm.

ESC noted that the ADAR relied upon one randomised controlled trial (RCT) comparing BST-Cargel+MF *vs.* MF (Stanish et al. 2013; n=80) over 12 months which had a potential conflict of interest because the sponsor owned the company at the time. ESC noted that there are serious concerns regarding bias with the data from the 5-year follow-up study (Shive et al 2015; n=67), primarily from high loss to follow-up (attrition bias). ESC also noted that the extension study by Shive et al. reasoned that significant loss to follow-up was partly because the original trial sponsor went bankrupt, and due to a period of transition from the current trial sponsor. ESC noted that the applicant agreed with the Commentary in the pre-ESC response, which considered that the concerns regarding bias with the data from the 5-year follow-up study are well justified. ESC considered that this limits the evaluation of clinical effectiveness to 12 months.

ESC also noted that risk of bias using GRADE was done incorrectly as it was done on study level not on outcome level, which also was noted in the Commentary.

Regarding comparative safety, ESC noted that the reported adverse events in the pivotal trial may be an over-estimate, as in the pivotal trial the product was delivered via an arthrotomy, rather than arthroscopically, which is what would be performed in Australian practice. ESC agreed with the Commentary who concluded that the clinical claim of non-inferior safety is justified for both the short term (12-month follow-up) and longer term (5-year follow-up).

Regarding comparative effectiveness, ESC noted the primary outcome of the pivotal trial was structural outcomes (degree of lesion fill %, repair cartilage T2 relaxation time and structural success [% fill > 70%]), as measured by magnetic resonance imaging (MRI). ESC noted that the claim of superior clinical effectiveness relied upon statistically significant differences in these outcomes, despite no known minimum clinically important differences (MCIDs). Moreover, ESC considered there was high uncertainty whether these structural outcomes on MRI are valid surrogates and correlate well enough with Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores, or with other patient-relevant outcomes (e.g. Short Form Health Survey- 36 item; SF-36). ESC noted for these patient-relevant outcomes there was no statistically significant difference between intervention and comparator, but noted the pivotal RCT was not powered to detect a difference, and thus the interpretation is subject to uncertainty. ESC noted the pre-ESC response, which the applicant considered there was moderate correlation between MRI parameters and clinical outcomes (Blackman 2013, de Windt 2013). However, ESC noted that Blackman 2013 included

different procedures and the clinical outcomes that are not direct measures of pain such as with the WOMAC and SF-36.

ESC also noted that the WOMAC score as an outcome had applicability concerns as it was validated in a different population: people with osteoarthritis of the hip and knee, rather than proposed population with focal cartilage lesions of the knee. Overall, ESC considered the superior effectiveness claim was uncertain, and in particular over the longer term, for which there was an absence of reliable data.

ESC considered the economic evaluations that included a trial-based cost-effectiveness analysis (CEA) and modelled cost-utility analysis (CUA) over 20 years as the base case model. ESC noted the CEA outcome was structural success, which ESC noted the applicant considered the incremental cost-effectiveness ratio (ICER) of $**redacted** per additional patient with lesion fill response to support value for money for CARGEL+MF *vs.* MF.

ESC noted the structure of the ADAR's CUA model, which was a Markov model with six health states, but effectively become condensed into a four-state model, including that the probability of regression of patients in the success health state is set to zero in the base case. ESC also noted that the base-case model extrapolates outcomes observed at 12 months over the entire 20-year period such that outcomes achieved at 12 months are maintained at the same level over a period of 20 years. ESC considered this to be highly unrealistic and noted that the independent expert advice provided in the Commentary suggested MF is not considered a long-term cure and often, patients go on to other procedures later in life. ESC also noted that the Commentary's additional analyses including more realistic scenarios with regression of treatment effect and subsequent treatments resulted in much higher ICERs (see Table 8).

ESC also noted additional uncertainty in the base-case model due to: the ADAR's decision to derive a binary measure of clinical success, via application of a correlation coefficient to the surrogate outcome (structural success); and quality-adjusted life year (QALY) was also derived via a series of transformations and assumptions which resulted in QALY gain for BST-Cargel over MF, which could not be validated with clinical evidence for patient-relevant outcomes.

ESC noted the Commentary made small technical changes to update the base case; however considered these did not reduce the uncertainty in the model. Overall, ESC agreed with the Commentary, which considered that the uncertainty in the economic model is largely a result of poor-quality clinical data, of which usable results are limited to 12-month structural outcomes, resulting in little confidence in the economic evaluation.

ESC noted that because BST-CARGEL is already reimbursed on the MBS, continued listing has no budget implications.

ESC considered that the out-of-pocket costs are likely to be high due to extensive physiotherapy rehabilitation, MRI and other tests, specialist visits, surgery, and hospital stays and potential loss of income.

ESC noted that the request is to evaluate CARGEL^{TM} for continued listing on the PL. ESC queried the level of evidence required to de-list a product that has been listed on the PL and reimbursed via MBS since 2015. However, ESC noted that the removal of items from the PL and decisions about ongoing PL listing will be made by the Minister's delegate based on PLAC advice and other factors.

ESC also considered that, if this were a new submission, more rigorous evidence would be required for decision making.

15.   Other significant factors

Nil.

16.   Applicant comments on MSAC's Public Summary Document

Smith & Nephew is disappointed with the outcome from this MSAC evaluation of CARGEL – a product which has been listed on the Prostheses List since 2015 and used globally without any safety nor effectiveness concerns to date. Smith & Nephew will work with the Prostheses List Advisory Committee and the Department of Health to ensure that Australian patients can continue to have equitable access to CARGEL via ongoing listing on the Prostheses List.

17.   Further information on MSAC

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