Australian Government

Medical Services Advisory Committee

Public Summary Document

Application 1578 – Arthroscopic injection of a bioadhesive hydrogel implant (JointRep™), in conjunction with microfracture, for treatment of osteochondral defects of the knee

Applicant: Device Technologies Australia

Date of MSAC consideration: MSAC 82nd Meeting, 29-30 July 2021

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

1. Purpose of application

An application seeking MSAC's advice to inform the Prostheses List Advisory Committee (PLAC) on the comparative safety, clinical effectiveness and cost-effectiveness of arthroscopic injection of a bioadhesive hydrogel implant (JointRep™), in conjunction with microfracture, for treatment of osteochondral defects of the knee was received from Device Technologies Australia 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 will advise the PLAC that there is insufficient evidence to demonstrate non-inferior safety, superior effectiveness and cost-effectiveness of JointRep™ in conjunction with microfracture compared with microfracture alone. In addition, MSAC concluded that the comparison of JointRep™ plus microfracture versus BST CarGel™ plus microfracture was uninformative and did not demonstrate non-inferior safety and effectiveness.

Consumer summary
This application is in response to a request from the Prostheses List Advisory Committee (PLAC) for MSAC to assess the safety, effectiveness and value-for-money of JointRep plus microfracture compared to microfracture alone, for the repair of cartilage defects of the knee. JointRep is already listed on the Prostheses List. Cartilage cushions the bones so that joints (such as the knee) can move easily. If cartilage is damaged, it can be difficult to regenerate (regrow) on its own. If damaged knee cartilage fails to repair using non-surgical treatments, surgical treatments such as microfracture may be considered. Microfracture is a surgical procedure where many small holes are made in the surface of the knee joint, which may stimulate a healing response, although the repair tissue can break down over time.

Consumer summary
JointRep is used together with microfracture and is claimed to help the healing process. JointRep is a gel that is designed to fill holes in the cartilage, building a scaffold that may help support the process of regrowing the knee cartilage. MSAC considered that the study using JointRep was poorly conducted and as such that the results were not reliable. Therefore, MSAC considered that there was not enough evidence to show that using JointRep in addition to microfracture was better or was good value for money compared with microfracture alone. **MSAC's advice to PLAC** MSAC advised PLAC that there was not enough evidence to demonstrate that using JointRep with microfracture is more effective or cost-effective compared to microfracture surgery alone. MSAC noted that a relevant clinical trial is currently underway (results expected December 2025), and that this trial may provide more evidence to inform JointRep's use in the future.

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

MSAC noted the purpose of the application was to provide advice to PLAC on the comparative safety, clinical effectiveness and cost-effectiveness of JointRep. JointRep is an injectable hydrogel scaffold that is listed on the Prostheses List (PL). MSAC noted that JointRep is used in conjunction with microfracture at the time of arthroscopy in patients with symptomatic focal osteochondral defects (Outerbridge Grade III or IV) defects of the knee to improve the growth of new cartilage. MSAC noted microfracture, with or without JointRep, is claimed under existing MBS items 49559, 49561 and 49562. MSAC noted these items descriptors may require amending, or a new item created, to define the population who are suitable for microfracture or for JointRep in conjunction with microfracture.

MSAC recalled that it had previously considered a similar prosthesis, BST-CarGel (MSAC application 1569), at the 79th MSAC meeting in July 2020. MSAC advised PLAC that BST-CarGel plus microfracture was not cost-effective as there was insufficient evidence to demonstrate non-inferior safety and superior effectiveness of BST-CarGel plus microfracture compared with microfracture alone. MSAC also recalled that in 2010, MSAC did not support public funding of autologous chondrocyte implantation (ACI) and matrix-induced autologous chondrocyte implantation (MACI) as it was not cost-effective (MSAC application 1140).

MSAC noted that JointRep would be used by orthopaedic surgeons only and that consultation feedback from the Australian Orthopaedic Association did not support the use of JointRep in conjunction with microfracture. MSAC noted the pre-MSAC response stated that several members of the Australian Knee Society (AKS), a subspecialty society of the AOA, will be participating in the JMAC trial[1], an international multicentre randomised controlled trial comparing JointRep with microfracture-alone (n=185, randomised 2:1).

MSAC noted the comparators (microfracture alone for population 1, lesions ≤2 cm^2; mosaicplasty, or microfracture in conjunction with BST-CarGel or Chondro-Gide for

[1] A Comparison of JointRep™ and Microfracture in Repair of Cartilage Lesions on the Femoral Condyle or Trochlea (JMAC) – NCTC 04840147
https://clinicaltrials.gov/ct2/show/NCT04840147?term=JointRep&draw=2&rank=1

population 2, lesions >2 cm^2) and the clinical management algorithm. MSAC considered the comparators to be appropriate, except for mosaicplasty, which is not commonly used in Australia and has little evidence to support its use. MSAC noted no evidence comparing JointRep with Chondro-Gide or mosaicplasty was presented in the ADAR.

MSAC noted the comparative clinical evidence for JointRep plus microfracture (n=46) compared with microfracture alone (n=23), comprised a single non-randomised unblinded study with 12-month, 24-month and 36-month (unpublished) follow-up data presented in the ADAR and 48-month follow-up data published in 2021. MSAC considered the JointRep study to be of very poor quality with a critical risk of bias. MSAC's confidence in the veracity of the JointRep study results was further eroded by data reporting errors and inconsistencies between and within study publications, reports, and the ADAR.

MSAC noted the ADAR claimed JointRep plus microfracture has non-inferior safety compared with microfracture alone. MSAC noted that no adverse events, complications, side effects or device deficiencies were reported in either arm of the JointRep study. However, MSAC noted the absence of safety events is not consistent with other microfracture studies, such as the study comparing BST-Cargel plus microfracture versus microfracture alone. MSAC considered the reliability of reporting safety outcomes in the JointRep study was uncertain and as such, MSAC considered the claim of non-inferior safety of JointRep plus microfracture compared to microfracture alone was uncertain.

Regarding comparative effectiveness of JointRep plus microfracture versus microfracture alone, MSAC noted the primary outcome reported in the JointRep study was the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score. Although the WOMAC scores for JointRep plus microfracture were lower (indicating improvement) than for microfracture alone, the benefits of both treatments declined over time. Noting the poor quality of the JointRep study, along with issues with the study design and data reporting, MSAC considered it was highly uncertain that any relative benefits observed in the intervention group can be attributed to JointRep. In addition, MSAC considered that data on safety and effectiveness of microfracture alone are limited, particularly long-term data, and that a randomised controlled trial of microfracture alone versus placebo should be undertaken to establish the benefit of microfracture. MSAC considered that the claim of superior effectiveness of JointRep was not supported due to the very low quality of the trial.

MSAC noted that the ADAR attempted to indirectly compare JointRep plus microfracture with BST-CarGel plus microfracture. MSAC considered that due to differences in populations, microfracture procedure and scoring systems used, the comparison was uninformative and did not demonstrate non-inferior safety and effectiveness of JointRep plus microfracture compared to BST-CarGel plus microfracture.

Overall, MSAC considered that the clinical evidence was limited and of very poor quality, leading to uncertain claims of superior effectiveness and non-inferior safety against microfracture alone. MSAC noted these uncertainties and issues with the quality of the clinical evidence flowed into the economic and financial analyses.

MSAC noted the cost-utility analysis comparing JointRep plus microfracture versus microfracture alone, in which the only cost difference was the cost of JointRep itself ($6,022) and estimated the incremental cost-effectiveness ratio (ICER) for JointRep plus microfracture versus microfracture alone to be $6,329. MSAC considered the economic model to be rudimentary with only two health states (alive or dead) and uninformative as the alive state did not distinguish between degree of treatment success. MSAC agreed with ESC that issues

with the low quality clinical evidence, applicability and transformation of WOMAC scores into health state utility values created unacceptably high uncertainty in the model. As such, MSAC considered there was insufficient evidence to demonstrate JointRep plus microfracture is cost-effective compared with microfracture alone.

MSAC noted the ADAR presented an economic analysis comparing JointRep plus microfracture versus BST-CarGel plus microfracture despite critical limitations in the clinical evidence which did not support a claim of non-inferiority. MSAC noted the pre-MSAC response reiterated that sensitivity results exploring the conversion factor for converting the BST-CarGel plus microfracture WOMAC score from VAS to Likert scale. However, MSAC agreed with ESC that the conversion of the WOMAC score from the VAS to the Likert scale created further uncertainty in the already uncertain translated health state utility values. Overall, MSAC considered the cost-effectiveness comparison of JointRep plus microfracture versus BST-CarGel plus microfracture to be uninformative.

MSAC considered the estimated implications to the PL through continued listing of JointRep were highly uncertain. MSAC noted the utilisation of JointRep was predicted to grow by an additional **redacted** procedures per year and the basis for this was reiterated in the pre-MSAC response. However, MSAC considered the predicted growth was uncertain given the historical market growth observed for prostheses like JointRep. MSAC also noted the discrepancy in utilisation estimates provided from the applicant's sales data (**redacted**) and PL billing data (**redacted**). MSAC queried whether the discrepancy may indicate a potential for JointRep to be used outside the proposed population (e.g. other joints) or whether repeat treatments would be performed. MSAC noted the uncertainty in the estimated impact to the MBS stemmed from uncertainty around whether the continued PL listing of JointRep may increase the uptake of the microfracture procedure. Overall, MSAC considered the estimated implications to the PL and MBS through continued listing of JointRep were highly uncertain.

MSAC noted that, if the PLAC recommend removing JointRep from the PL in response to MSAC's advice that JointRep plus microfracture is not cost-effective compared to microfracture alone, consumers will face substantial out-of-pocket costs if they choose to use JointRep in conjunction with microfracture. MSAC noted PLAC could choose to consider the applicant's pre-MSAC response, which acknowledged the weaknesses of the JointRep study and offered to **redacted** the cost of JointRep to $**redacted** until the interim results of JMAC trial (expected 2023) can be used to conduct a new economic analysis. MSAC's advice to PLAC on the **redacted** fee option is that while **redacted** the benefit of JointRep to **redacted** the ICER, the cost-effectiveness of JointRep at this **redacted** benefit remains uncertain as the issues with the low-quality clinical evidence and unacceptably high model uncertainty remain.

MSAC considered that any resubmission should present robust, high quality clinical trial data on the safety and effectiveness of JointRep plus microfracture and present a revised economic model that address the concerns raised (e.g. captures treatment success, re-operation, etc). MSAC also noted that the JMAC trial does not include a placebo arm, as such would not address MSAC's concern that there is insufficient evidence that microfracture is safe and effective and whether using prostheses such as JointRep in conjunction with microfracture may be adding costs to a procedure that is harmful. Therefore, MSAC also considered that any resubmission would need to present clinical trial evidence addressing the safety and effectiveness of microfracture alone which could be achieved by including a placebo arm in the JMAC trial. Alternatively, the need for a clinical trial on the long-term safety and

effectiveness of microfracture could be referred to the Medical Research Future Fund (MRFF).

4. Background

This is the first submission (Applicant Developed Assessment Report [ADAR]) for JointRep, in conjunction with microfracture, for treatment of osteochondral defects of the knee.

JointRep was listed on the Prostheses List (PL) in July 2019 (Billing Code DE681; $6,022) in the same PL grouping (with the same benefit) as BST-CarGel, which was included on the PL in 2015 (Billing Code SL072; $6,022). PLAC noted that JointRep and BST-CarGel are similar to autologous chondrocyte implantation (ACI) and matrix-induced autologous chondrocyte implantation (MACI), which MSAC have previous assessed not suitable for public funding (MSAC application 1140 Public Summary Document [PSD] 2010).

The PLAC recommended a health technology assessment (HTA) via MSAC for JointRep to determine the clinical effectiveness and cost-effectiveness of this product, and to clarify the appropriate MBS item.

Other MSAC applications for chondral defects of the knee
MSAC application 1140 for MACI and 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 1140 PSD 2010).

MSAC application 1569 for chitosan-based cartilage bio-matrix implant (BST-CarGel), in conjunction with the marrow stimulation technique (microfracture), for repair of focal cartilage defects was also referred to MSAC by PLAC for advice on the clinical effectiveness and cost-effectiveness of BST-CarGel. MSAC application 1569 was considered by MSAC in July 2020. MSAC advised PLAC that BST-CarGel was not cost-effective as there was insufficient evidence to support non-inferior safety and superior effectiveness of BST-CarGel compared with microfracture alone (MSAC application 1569 PSD 2020).

5. Prerequisites to implementation of any funding advice

JointRep was included in the Australian Register of Therapeutic Goods (ARTG) in April 2019. The intended purpose for JointRep as per ARTG entry 316444 is “the treatment of isolated cartilage defects Grade III and IV (ICRS/ Outerbridge scores) of the knee joint in combination with microfracture surgery. Use of the implant is not appropriate in the presence of more generalised degeneration, meniscal deficiency or established osteoarthritis”.

The commentary noted that the proposed population in the ADAR is consistent with the intended purpose specified in the ARTG entry for JointRep but refers to ‘symptomatic focal osteochondral defects’ rather than ‘isolated cartilage defects’.

6. Proposal for public funding

The ADAR claimed that the microfracture procedure in conjunction with JointRep is adequately covered by existing MBS items (49559, 49561 and 49562).

The commentary noted that the descriptors of the existing MBS items do not define the population who are suitable (or unsuitable) for microfracture or for JointRep in conjunction with microfracture. It is not known whether current use of JointRep in conjunction with microfracture is limited to the population who are most likely to benefit from the intervention.

Although not requested by the applicant, MSAC may wish to consider whether the current MBS items should be amended or if a new MBS item should be created, to capture all content/contraindications/exclusion criteria relating to the implant as suggested by PASC.

Other funding
PLAC will consider the PL implications for JointRep after receipt of MSAC advice on the clinical effectiveness and cost-effectiveness of JointRep in conjunction with microfracture.

7. Summary of public consultation feedback/consumer Issues

Consultation feedback was received from the Australian Orthopaedic Association (AOA) which was not supportive of the intervention. The AOA claim the evidence of benefit in the short-term is not convincing, there is no evidence on the long-term benefit, other treatments are more effective, the cost is high and there is probability of widespread use outside of the proposed population. The feedback suggested other comparators and recommended the need for longer-term outcome studies on microfracture, and that the MBS item 49559 may be more appropriate.

No consumer feedback/consumer comments were received for this application.

8. Proposed intervention's place in clinical management

Description of Proposed Intervention
JointRep is an arthroscopically injectable thermo-gel implant with a glucosamine polysaccharide formulation. It is designed to fill and resurface cartilage defects, forming a scaffold *in situ* that provides support for progenitor cells. JointRep is used in conjunction with microfracture, which is an arthroscopic bone marrow stimulating articular repair technique that involves drilling multiple holes or 'microfractures' in the underlying bone to allow recruitment of autologous bone marrow cells into the vicinity of the defect.

Description of Medical Condition
The proposed population for which JointRep is indicated is patients with symptomatic focal osteochondral defects (Outerbridge Grade III or IV) of the knee, having failed conservative treatment and being indicated for surgery; excluding individuals with more generalised degeneration, meniscal deficiency or established osteoarthritis. Within the population, there are two sub-populations for whom treatment is different depending on their defect size:

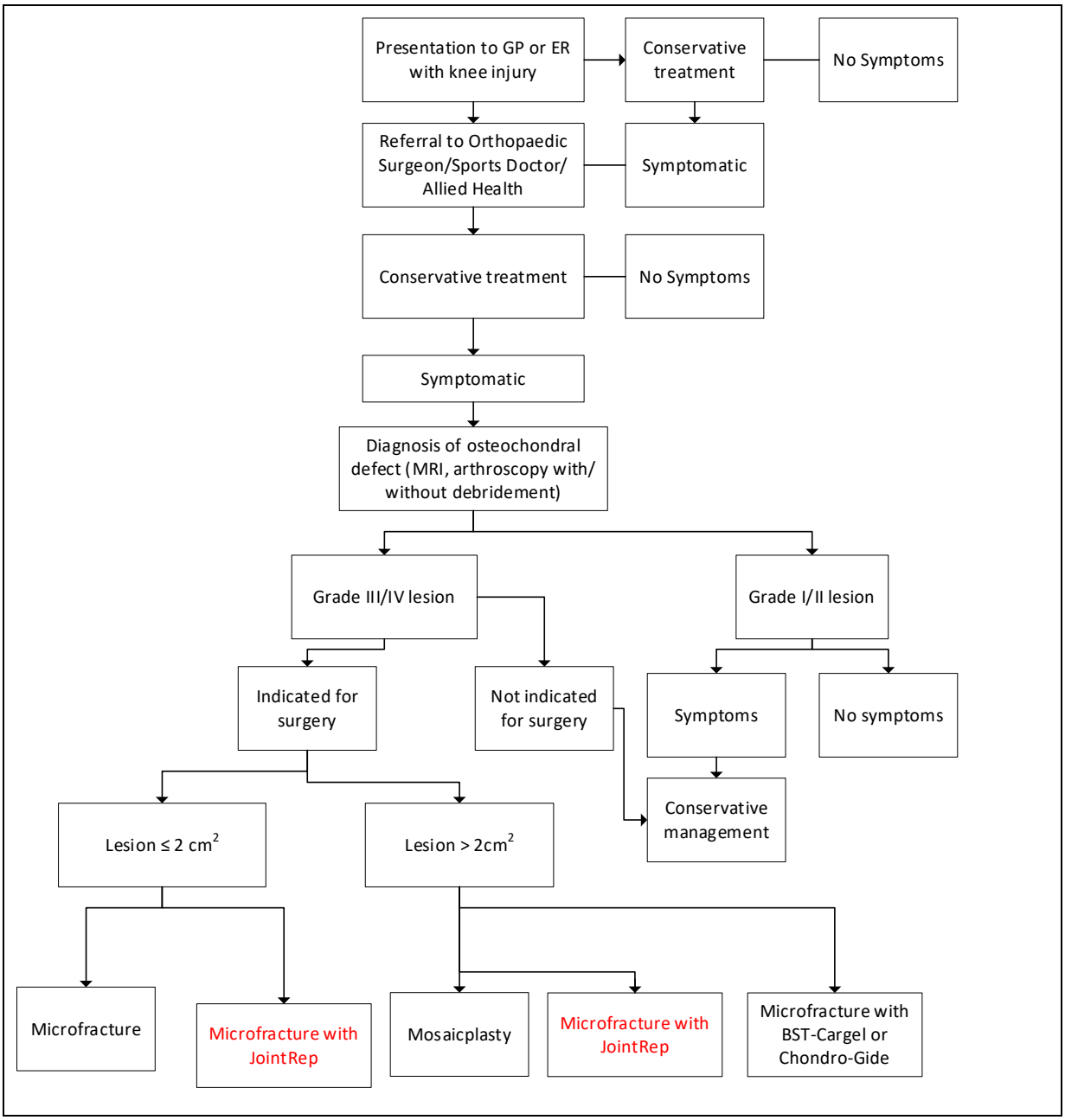
1. patients with a defect ≤ 2 cm^2 in size
2. patients with a defect > 2 cm^2 in size.

There are no official clinical guidelines in Australia for the management of chondral injuries. The clinical management algorithm and the proposed place of JointRep in conjunction with microfacture is presented in Figure 1.

The commentary noted that the clinical algorithm does not show microfracture alone as an appropriate comparator for the larger lesion size subpopulation (> 2 cm^2). The algorithm does not include rehabilitation, which is highly individualised with tailoring of the weight bearing

status progression and the subsequent exercise program depending on the size and location of the defect. The algorithm does not show that a second surgical repair may be attempted in cases where the repair fails or symptoms recur. It is unclear whether JointRep would be used during reoperation.

Figure 1 Clinical management algorithm/s for the proposed new intervention relative to current clinical practice



Source: Figure 3 (p35) of the ADAR
Abbreviations: ACI = autologous chondrocyte implantation; ER = emergency room; GP = general practitioner; MRI = magnetic resonance imaging; OATS = osteochondral autograft transfer.
Note 1: The proposed intervention is indicated in red.
Note 2: Microfracture alone is also a comparator for lesions > 2 cm^2 (not shown).

9. Comparator

The comparators in the ADAR are:

- Microfracture alone
- Microfracture in conjunction with BST-CarGel (MSAC application 1569).

The comparators in the ADAR deviated from the PICO Confirmation for MSAC 1578. The ADAR did not include mosaicplasty as a comparator, claiming that mosaicplasty is a technically demanding procedure and is not frequently used in Australia. Other scaffold products were not included as a comparator in the ADAR, including Chondro-Gide as the ADAR claimed it is used rarely, if ever, in Australia. PASC acknowledged it is not useful to assess comparators not in use in Australia (PICO Confirmation p.8).

Although ACI and MACI (MSAC application 1140) were not specified as comparators in the PICO Confirmation, the PICO Advisory Sub-Committee (PASC) requested that any comparative evidence be presented, if available, for ACI/MACI versus JointRep in conjunction with microfracture. The commentary noted that no relevant evidence was identified.

10. Comparative safety

JointRep plus microfracture versus microfracture alone
One non-randomised unblinded study comparing JointRep in conjunction with microfracture (n=46) versus microfracture alone (n=23) was included in the ADAR (Table 1). The commentary found the JointRep study to have a critical risk of bias, noting concerns regarding:

- inconsistent recruitment to control arm
- between group differences in baseline patient characteristics
- undisclosed number of study participants had osteoarthritis
- undisclosed number of study participants underwent simultaneous surgical interventions of the knee
- use of a non-standard rehabilitation protocol that may have led to unfavourable clinical outcomes for the control group, and
- inadequate, incorrect or contradictory data reporting.

The pre-MSAC response acknowledged that there are shortcomings in the JointRep study. The applicant considered that: the protocol of weight bearing was not necessarily inconsistent with current practice, patients with arthritis had focal lesions that were secondary to primary disease and not diffuse 'wear and tear' associated with primary arthritis, and clarified the microfracture technique used.

Table 1 Key features of included evidence comparing JointRep plus MF with MF alone

Trial/Study	Design/ duration	Risk of bias†	Patient population	Outcome(s)	Outcome used in economic model
Pipino 2019 (study publication) Interim Study Report (Pipino 2018) Unpublished Patient-level Data and Analysis file	Non-randomised, single-centre controlled study N=69 24 months (Pipino 2018,2019) 36 months (unpublished patient-level data)	Critical (ROBINS-I)	Outerbridge Grade III-IV OCDs of the knee secondary to primary OA or trauma and refractory to conservative measures Age 26-72 (mean 55) years 58% male BMI not reported JointRep n=46 Control n=23	WOMAC	WOMAC

Source: Table 2,pxv of the commentary
Abbreviations: BMI = body mass index; OA = osteoarthritis; OCD = osteochondral defect; MF = microfracture; ROBINS-I = Risk of Bias in Non-randomised Studies of Interventions; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index
† Assessed for commentary (refer to Attachment B of the commentary). The ADAR reported 'acceptable' risk of bias using the SIGN checklist.

No adverse event, complication, side effect or device deficiency was reported in either group of the JointRep study during the 12-month and 24-month follow up periods. The ADAR noted that two patients discontinued from the study due to trauma unrelated to the intervention, one due to a car accident and the other due to a tibial plateau fracture.

The commentary noted that the absence of any adverse events over the reporting period of 24 months suggests that the mechanism for reporting and recording adverse events may have been inadequate; and/or the focus was solely on serious adverse events or adverse events that were considered by the investigators to be unanticipated and device-related.

JointRep plus microfracture versus BST-CarGel plus microfracture
No studies were identified that directly compared JointRep plus microfracture versus BST-CarGel plus microfracture. The ADAR included two studies to support an indirect comparison using a common comparator (microfracture alone) (Table 2). These publications have been considered previously by MSAC (PSD for Application 1569, July 2020).

Table 2 Key features of included evidence comparing BST-CarGel plus MF with MF alone

Trial/Study	Design/ duration	Risk of bias (WOMAC only)†	Patient population	Key outcome(s)	Outcome used in economic model
Stanish 2013 (NCT0031423)	International multicentre RCT N = 80 12 months	Some concerns (RoB 2.0)	Single, focal cartilage lesion on the femoral condyles and moderate knee pain; full-thickness Grade 3 or 4 according to the ICRS (3A, 3B, 3C, 3D and 4A) Age 18-55 (mean 36) years BST-CarGel n=41 Control n=39	Repair tissue quantity and quality WOMAC (VAS) SF-36	WOMAC (VAS converted to Likert)
Shive 2015	Extension study N = 67 5 years	Serious (ROBINS-I)	Subjects enrolled in Stanish 2013 RCT who agreed to participate in follow up For WOMAC results: BST-CarGel n=33 Control n=26	Repair tissue quantity and quality WOMAC SF-36	WOMAC (VAS converted to Likert)

Source: Table 3 pxvi of the commentary
Abbreviations: ICRS = International Cartilage Repair Society; MF = microfracture; RCT = randomised controlled trial; RoB 2.0 = Cochrane Risk of Bias Tool for Randomised Trials (2.0); ROBINS-I = Risk of Bias in Non-randomised Studies of Interventions; SF-36 = 36-item Short Form health survey; VAS = visual analogue scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index
† Assessed for commentary (refer to Attachment B). The ADAR reported 'some concerns' using the Cochrane Risk of Bias Tool for the RCT and extension study.

Serious adverse events were reported for five patients (12.2%) in the BST-CarGel plus microfracture group (four of these were procedure-related and one was device-related) and for one patient (2.6%) in the microfracture group (not procedure-related). The commentary noted that BST-CarGel was administered through a mini-arthrotomy, so more procedure-related events may be expected compared with interventions administered arthroscopically.

The ADAR acknowledges that it is difficult to compare the safety results across the two studies as it was clear that different methods of reporting adverse events were used.

11. Comparative effectiveness

JointRep plus microfracture versus microfracture alone
The overall trend in each of the subscales and the total WOMAC score was large score reductions at 6 months, with a statistically significant difference between groups for all but the pain subscale. At all subsequent timepoints, between-group differences were statistically significant, with sustained or continued score reductions in the JointRep plus microfracture group but increasing scores over time in the control group (Table 3). There is uncertainty around the durability of benefits in the JointRep plus microfracture group as scores appear to be trending up slightly at 36 months.

The commentary considered that the description of findings should be considered in light of the critical risk of bias. There is a high degree of uncertainty that any relative benefits in the intervention group can be attributed to the JointRep device, and whether the lack of durability of early improvements in the control group may have been influenced by allowing weight bearing as tolerated immediately after the surgery, contrary to well-established standard of care. By contrast, improvements in the microfracture group observed in the BST-CarGel trial were sustained through to the last follow up at 60 months, albeit with uncertainties arising from loss to follow up.

Table 3 Total WOMAC scores for JointRep with MF compared with MF alone

Total WOMAC score (scale 0-96 normalised to 0-100)	Risk of bias†	JointRep with MF	MF alone	Absolute difference between groups	p-value
		mean ±SD (95% CI)	mean ±SD (95% CI)	mean difference ±SE (95% CI)	
Baseline	Critical	**n=46** 58.9 ±10.9 (55.7 to 62.1)	**n=23** 57.0 ±4.1 (55.2 to 58.8)	1.88 ±1.82 (-1.69 to 5.45)	p=0.306
6 months	Critical	7.4 ±9.1 (4.7 to 10.1)	28.4 ±4.4 (26.5 to 30.4)	-17.17 ±1.11 (-19.35 to -15.00)	p<0.0001
12 months	Critical	4.8 ±7.4 (2.6 to 7.0)	42.3 ±15.0 (35.8 to 48.8)	-37.55 ±3.32 (-44.05 to -31.04)	p<0.0001
24 months	Critical	**n=44** 2.9 ±5.9 (1.1 to 4.6)	**n=23** 48.3 ±13.3 (42.5 to 54.0)	-45.41 ±2.91 (-51.12 to -39.71)	p<0.0001
36 months	Critical	4.1 ±7.9 (1.3 to 6.9)	49.5 ±13.3 (42.7 to 56.2)	-45.38 ±3.02 (-51.30 to -39.47)	p<0.0001

Source: Table 4, pxviii of the commentary
Abbreviations: CI = confidence interval; MF=microfracture; SD = standard deviation; SE = standard error; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index
Note: Subscale scores are reported in Section B.6.
† Assessed for commentary

The pre-ESC response indicated that 4-year results are available for the treatment group from the JointRep study (Indelli et al. 2021[2]). The applicant noted that the WOMAC scores were maintained at 4 years demonstrating a durable treatment effect.

[2] Indelli PF et al 'Microfracture and Hydrogel Scaffolds for the Treatment of Osteochondral Injuries of the Knee: Clinical Results at 4 Years Follow-up' J Clin Med Res. 3032;2 (1): 1-13

The pre-MSAC response reiterated that an ongoing international (Australian/Canadian/New Zealand) clinical trial may address concerns raised in the commentary. *'A Comparison of JointRep™ and Microfracture in Repair of Cartilage Lesions on the Femoral Condyle or Trochlea (JMAC)'* is a multicentre randomised controlled trial (RCT) to assess the effectiveness and safety of JointRep (NCT04840147). The primary outcome is percentage lesion fill (24 months post procedure) measured by magnetic resonance imaging (MRI). Secondary outcomes included VAS pain score, MRI parameters, treatment failure, knee injury and osteoarthritis outcome score (KOOS), tenger activity scale, safety and EQ-5D. The estimated enrolment is 185 participants randomised 2:1 to either microfracture plus JointRep or microfracture alone. The post-operative rehabilitation regime will be followed, amongst it the progression to full weight bearing and the return to previous activity level. The estimated study completion date is December 2025.

JointRep plus microfracture versus BST-CarGel plus microfracture

The ADAR does not compare the baseline characteristics for the control groups in the JointRep study and BST-CarGel trial, nor does it present WOMAC scores for the BST-CarGel control group (microfracture alone). Therefore, the commentary considered it was not possible to confirm the appropriateness of the indirect comparison of the intervention groups in these studies. Differences between the studies were noted with regard to eligibility criteria, demographics, microfracture technique, simultaneous surgical treatments and rehabilitation protocols, which impacts the validity of the indirect comparison.

The BST-CarGel trial used a visual analogue scale (VAS) format for WOMAC scoring whereas the JointRep study used the Likert scale. In the absence of any available published algorithms for VAS to Likert transformation, the ADAR proposed a conversion factor computed by dividing the maximum plausible value for sub-scores of the Likert scale by the corresponding maximum values of the VAS scale. The commentary considered the proposed conversion factor of 0.4 is problematic.

The comparison of JointRep plus microfracture and BST-CarGel plus microfracture results presented by the ADAR are reproduced in Table 4. These results are mean scores for the intervention group at particular time points; they do not account for differences between the JointRep plus microfracture and BST-CarGel plus microfracture groups at baseline.

Table 4 Comparison of JointRep and BST-CarGel mean WOMAC scores at various time points

Outcome measure	JointRep+MF 12 months	BST-CarGel+MF 12 months	JointRep+MF 36 months	BST-CarGel+MF 60 months
	Mean (±SD)	Mean converted from VAS to Likert	Mean (±SD)	Mean converted from VAS to Likert
Pain	~~0.9 ±2.3~~ *1.1 ±1.4*[a]	2.1	0.9 ±2.3	2.3
Stiffness	~~0.4 ±1.2~~ *0.5 ±1.3*[a]	1.8	0.4 ±1.2	1.8
Physical	~~2.6 ±4.3~~ *3.2 ±5.1*[a]	8.7	2.6 ±4.3	~~8.2~~ *8.8*[b]
Total	~~3.9 ±7.8~~ *4.8 ±7.4*[a]	12.7	4.1 ±7.9	~~12.3~~ *12.7*[b]

Source: Table 15 of the ADAR (p.56), with commentary corrections in italics [Table 5, pxix of the commentary]
Abbreviations: MF=microfracture; SD = standard deviation; VAS = visual analogue scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index
Note: WOMAC scores for BST-CarGel were converted from VAS to Likert by multiplying by 0.4 (ADAR p.57).
a Corrected using data in Table 14 of the ADAR (p.56).
b Corrected using data on p.57 of the ADAR.

The ADAR acknowledges that no conclusions can be drawn regarding the comparative effectiveness of JointRep plus microfracture and BST-CarGel plus microfracture on the basis

of the data available. The commentary considered that this conclusion was appropriate as the common comparator groups were not exchangeable between the JointRep and BST-CarGel studies. Due to overall differences between the two studies in terms of eligibility criteria, demographics, microfracture technique, simultaneous surgical treatments and rehabilitation protocols, any indirect comparison of the intervention groups has limited validity. The commentary also considered a meaningful comparison of outcomes is also prevented due to serious limitations with the conversion of VAS scores to align with Likert scores and the lack of change from baseline data for the JointRep study.

Clinical claim

JointRep plus microfracture versus microfracture alone

On the basis of the benefits and harms reported in the evidence base, the ADAR proposes that, relative to microfracture alone, JointRep in conjunction with microfracture has non-inferior safety and superior effectiveness.

The commentary considered the evidence presented in the ADAR consists of a single, small, non-randomised study with very serious risk of bias. The study population is poorly defined and poorly described and does not align well with the PICO population. The claim of non-inferior safety is not justified; due to concerns regarding the reliability of the reporting of AE in the JointRep study. While a large effect size is demonstrated in relation to the primary effectiveness outcome (self-reported WOMAC score), the study design, execution and reporting is too problematic to provide any reliable evidence of treatment effect. On this basis, the clinical claim of superior effectiveness is not justified.

JointRep plus microfracture versus BST-CarGel plus microfracture

The ADAR presents no interpretation of the clinical evidence of the comparative effectiveness of JointRep plus microfracture versus BST-CarGel plus microfracture. The ADAR states that "it is possible that JointRep plus microfracture and BST-CarGel plus microfracture will have a similar level of effectiveness".

Translation issues

Applicability

The ADAR acknowledges applicability issues between the JointRep study population and the patient population defined in the PICO, but notes that it is the most applicable published information available. The WOMAC outcome measure fulfils the PASC recommendation for consistency of outcomes between BST-CarGel plus microfracture and JointRep plus microfracture. However, the commentary considered its applicability to the PICO population with focal chondral defects is unclear, as the WOMAC has been validated in a population with hip and knee osteoarthritis, and patients with established osteoarthritis were specifically excluded from the PICO population.

Extrapolation

The base case analysis of 3 years is within available follow up data. Extrapolation beyond the available data assumes no further change in utility for either intervention or comparison. The commentary considered that the direction of bias this introduces is unclear. This is because the microfracture procedure is not considered to be a long-term curative intervention and subsequent interventions may be required.

Transformation

The WOMAC total scores were mapped to 5-dimension EuroQol (EQ-5D) using Australian utility values to allow calculation of quality-adjusted life years (QALYs). The commentary

considered that the approach taken was transparent and involved relevant expertise. Potential issues with this approach relate to whether WOMAC responses in an Australian population would correlate to EQ-5D responses in the same way as in the Spanish population preparing for joint replacement surgery, in which this approach was originally applied.

12. Economic evaluation

The economic evaluation is summarised in Table 5.

Table 5 Summary of the economic evaluation

Perspective	Australian health care system
Comparators	Microfracture alone, BST-CarGel + microfracture
Type of economic evaluation	Cost-utility analysis
Sources of evidence	~~RCT~~, Economic evaluation studies *The evidence for JointRep is from a non-randomised study. The evidence for BST-CarGel is an RCT (12 months) and an extension study thereafter.*
Time horizon	3 years in base case
Outcomes	QALYs gained
Methods used to generate results	Decision analytic Markov model
Health states	Alive, Dead
Cycle length	12 months
Discount rate	5% per annum (0 and 3.5% per annum tested in scenario analyses)
Software packages used	Excel 2016

Source: Table 6, pxx of the commentary
Abbreviations: QALY = quality-adjusted life year; RCT = randomised controlled trial

The commentary noted the time horizon was within available data for the main comparison. The potential need for reoperation was considered in a scenario analysis but used indirect data. The approach to economic evaluation, especially for the base case, was very simple which may limit the usefulness of the model. However, to increase the number of health states (e.g., 'treatment success' versus chronic or intermittent pain) would necessitate the use of data from other interventions to inform transition probabilities, further increasing uncertainty of the outputs.

Model utility values were derived from a transformation of WOMAC subscales and total score, adjusted for age and sex, to Australian time trade-off derived EQ-5D-based utility values. The disutility values for total knee arthroplasty were derived from the study by Mather et al. 2014 (Table 6).

Table 6 Model utilities

Model cycle	JointRep + microfracture		Microfracture alone		BST-CarGel + microfracture	
	Mean WOMAC Likert score (SD)	Estimated utility value*	Mean WOMAC score (SD)	Estimated utility value*	Mean WOMAC score**	Estimated utility value*
0 months (Baseline)	56.5 (10.5)	0.419	54.7 (4)	0.479	VAS:108.3 Likert:43.3	0.553
0-6 months	7.1 (8.8)	0.899	27.3 (4.3)	0.709	NR	NR
6-12 months	4.6 (7.1)	0.915	40.7 (14.4)	0.599	NR	NR
Cycle 1 (Year 1)	-	0.907	-	0.654	VAS:31.7 Likert:12.7	0.848
Cycle 2 (Year 2)	2.8 (5.6)	0.926	46.3 (12.8)	0.548	Same as cycle 1	Same as cycle 1
Cycle 3 (Year 3)	3.9 (7.6)	0.920	47.5 (12.8)	0.541	Same as cycle 1	Same as cycle 1

Source: Table 40, p87 of the commentary
Abbreviations: NR = not reported; SD = standard deviation; VAS = visual analogue scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis index
*Reported as a weighted average (weighted by gender distribution in each treatment arm).
**WOMAC Likert score = WOMAC VAS score x 0.4 (conversion factor based on maximum plausible sub-scores of WOMAC versions).

The commentary considered that comparing utility values between JointRep with microfracture and microfracture alone may be subject to confounding, due to the non-randomised nature of the study, multiple identified sources of potential bias, and inadequate reporting. Although a large difference in treatment effect was reported between the intervention and comparison groups, these data are not reliable due to significant between-group differences in baseline characteristics, heterogeneity within the control group at baseline, and a non-standard rehabilitation protocol that may have led to unfavourable clinical outcomes for the control group. This uncertainty carries over to the interpretation of the reported ICERs, to the extent the utility values are a determinant of the QALYs gained.

The overall costs and outcomes, and incremental costs and outcomes as calculated for the intervention and comparator in the model are shown in Table 7.

Table 7 Base case incremental cost-effectiveness ratio QALY outcomes

Treatment	Total cost	Incremental cost		Total effectiveness (QALYs)	Incremental effectiveness		ICER	
		vs MF alone	vs BST-CarGel + MF		vs MF alone	vs BST-CarGel + MF	vs MF alone	vs BST-CarGel + MF
JointRep + MF	$12,758	$6,022	$0	2.61	0.95	0.20	$6,329	$0
MF alone	$6,737	-	-	1.66	-	-	-	-
BST-CarGel + MF	$12,758	-	-	2.41	-	-	-	-

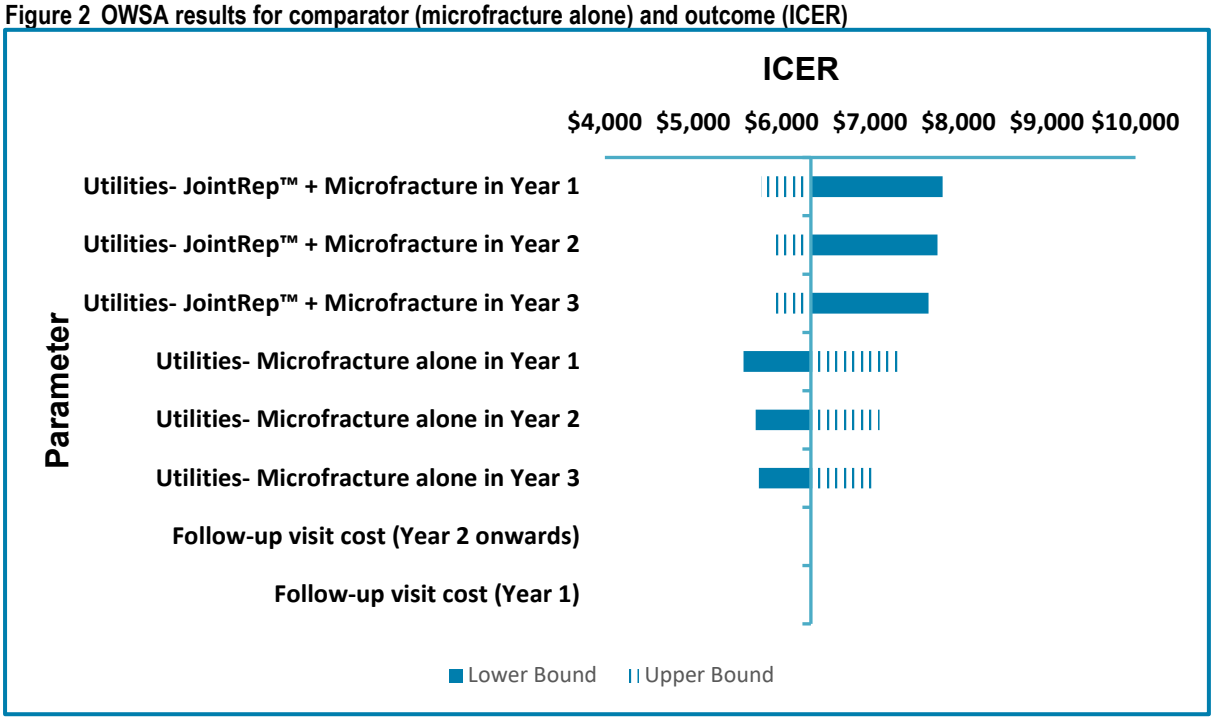
Source: ADAR Table 27, p.83
Abbreviations: ICER = incremental cost-effectiveness ratio; MF = microfracture; QALY = quality-adjusted life year

The commentary considered that the costs were broadly reasonable, albeit with fairly limited consideration of downstream interventions required, and those relying on indirect data. The quality of the available data and the potential issues with applicability to the PICO population mean the claim of effectiveness is subject to considerable uncertainty and – as the WOMAC outcome measures drives the effectiveness measure of QALYs in the economic evaluation –

the magnitude and direction of the incremental cost-effectiveness ratio (ICER) are similarly subject to considerable uncertainty.

One-way sensitivity analyses (OWSA) were conducted to identify the key drivers of the economic evaluation and to assess the impact of changing the parameter values on model results. The analyses evaluated lower and upper bounds for each model parameter considered. The model varied input parameters by plus and minus 20% of the base case parameter value. It was assumed that a range of 20% variation would capture deviation from the base case values. The results of OWSA were plotted on a tornado diagram to provide a visual representation of sensitivity of model results to input parameters. The modelled results were sensitive to utility inputs and were not affected by follow up visit costs (Figure 2).

Figure 2 OWSA results for comparator (microfracture alone) and outcome (ICER)



Source: *Compiled from ADAR economic model*[a]
Abbreviations: ICER = incremental cost-effectiveness ratio; OWSA = one-way sensitivity analyses; TKA = total knee arthroplasty
[a] *The OWSA for the proportion of patients receiving TKA in both model arms were removed as the base case value was 0%, and thus there was no variation in the upper and lower estimates which varied plus and minus 20% of the base-case parameter value*

Several scenario analyses were performed to understand the effect of various model settings or assumptions of the analysis on model results. The results showed that including one patient with TKA in the intervention arm (base case model did not include patients with TKA in either model arm) and excluding patients with lesion size ≤ 2 cm^2 yielded only a small increase in the ICER, and the remaining alternative scenarios yielded a decreased ICER relative to the base case analysis (Table 7).

Table 8 Scenario analysis results for comparator, microfracture alone

Base case setting/ value	Scenario setting/ value	ICER	% change from base case ICER
Base case	NA	$6,329	NA
Not including patients with TKA in the analysis	Including one patient with TKA in JointRep + MF arm	$6,814	8%
Including all patients from Pipino et al. (2019) study	Excluding trial patients with lesion size ≤ 2 cm^2	$6,414	1%
Not including proportion of patients undergoing reoperation	Reoperation rates at a time horizon of 15 years: JointRep + MF 2.44%[a] MF alone 18.92%[a]	-$11 *$44 if using lower limit of re-estimated cost of TKA*	-100%
Time horizon: 3 years	Time horizon: 5 years	$3,809	-40%
	Time horizon: 10 years	$2,088	-67%
Discount rate: 5%	Discount rate: 0%	$5,997	-5%
	Discount rate: 3.5%	$6,230	-2%

Source: ADAR Table 28, pp.85-86, with commentary in italics
Abbreviations: ICER = incremental cost-effectiveness ratio; MF = microfracture; NA = not applicable; TKA = total knee arthroplasty
a The reoperation values were taken from Frappier et al. 2014 (Table 2) comparing BST-CarGel + microfracture with microfracture alone

The pre-MSAC response reiterated claims that JointRep plus microfracture is highly cost-effective compared to microfracture alone, arguing that economic model presented in the ADAR is both conservative and in-line with published economic models. Regarding concerns raised with the transformation of WOMAC scores into health state utility values, the applicant:

- conducted additional scenario analyses where the incremental benefit is reduced by 10%, 25%, 50% and 75% resulting in ICER of $7,033, $8,439, $12,659 and $25,318 per QALY.
- performed additional sensitivity analyses related to varying the conversion factor used to transform the WOMAC VAS scores to Likert scores for the economic evaluation of JointRep versus BST-Cargel. This showed that JointRep dominates BST-Cargel with a range of VAS to Likert conversion factors.

The pre-MSAC response also reiterated its proposal for JointRep continue to be included on the PL but at a **redacted** benefit of $**redacted** until the JMAC trial reports results (December 2025). **Redacted**. The applicant provided additional sensitivity analyses using the **redacted** benefit of $**redacted** and reducing the incremental QALY gained by 10%, 25%, 50% and 75% resulting in ICER of $**redacted**, $**redacted**, $**redacted** and $**redacted**.

13. Financial/budgetary impacts

Real-world Australian utilisation data (Commercial-In-Confidence) was used as the basis to forecast the financial implications of continued use of JointRep via the MBS (Table 9) and the PL (Table 10).

For the estimated impact on the MBS (Table 9), the base case financial estimates acknowledge a small increased risk of TKA with the use of JointRep (one patient in the JointRep study) and a lower risk of reoperation when JointRep is used in conjunction with microfracture (applied in Year 3 and Year 5). The commentary noted that the risk of reoperation was taken from a study of BST-CarGel rather than JointRep.

Table 9 Total cost impact to the MBS of continued listing of JointRep and the incremental costs for reoperation – Base case using sales data (Commercial-In-Confidence)

	MBS item(s)	Year 1 2021	Year 2 2022	Year 3 2023	Year 4 2024	Year 5 2025
Estimated utilisation of JointRep						
Base case		**redacted**	**redacted**	**redacted**	**redacted**	**redacted**
Cost per year (base case)						
Microfracture procedure	MBS 49562	**$redacted**	**$redacted**	**$redacted**	**$redacted**	**$redacted**
Anaesthesia	MBS 17610 MBS 21382 MBS 23065	**$redacted**	**$redacted**	**$redacted**	**$redacted**	**$redacted**
Assistant	MBS 51303	**$redacted**	**$redacted**	**$redacted**	**$redacted**	**$redacted**
Follow-up visits[a]	MBS105	**$redacted**	**$redacted**	**$redacted**	**$redacted**	**$redacted**
Follow-up MRI[a]	MBS 63328	**$redacted**	**$redacted**	**$redacted**	**$redacted**	**$redacted**
Knee arthroplasty costs[b]	MBS 17610 MBS 21402 MBS 23085 MBS 49518 MBS 51303	**$redacted**	**$redacted**	**$redacted**	**$redacted**	**$redacted**
Reoperation costs[a,c]	As for initial procedure	**$redacted**	**$redacted**	**$redacted**	**$redacted**	**$redacted**
TOTAL	**-**	**$redacted**	**$redacted**	**$redacted**	**$redacted**	**$redacted**

Source: Table 10, pxxiii-xxiv of the commentary with utilisation estimates from Table 44, p93 of the commentary
Abbreviations: MBS = Medical Benefits Schedule; MRI = magnetic resonance imaging
Note: Rounding has been applied in the table.
a The ADAR applies a 75% benefit rather than 85% benefit for follow-up visits and MRI. These costs have not been corrected in the table.
b The calculations assume the risk of TKA is 0.02174 or 1/46 (Pipino 2019).
c The reoperation rates were taken from a study comparing BST-CarGel + microfracture with microfracture alone (Frappier et al. 2014).

The estimated utilisation and the cost to the PL of continued listing of JointRep is shown in Table 10. Costs relate to the JointRep prosthesis only and do not incorporate use of other prostheses (e.g., for total knee arthroplasty [TKA]).

Table 10 Estimated utilisation and cost to the Prostheses List of continued listing of JointRep – Base case using sales data (Commercial-In-Confidence)

Cost per year	Year 1 2021	Year 2 2022	Year 3 2023	Year 4 2024	Year 5 2025
Estimated utilisation of JointRep	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**
Estimated cost of JointRep	**$redacted**	**$redacted**	**$redacted**	**$redacted**	**$redacted**

Source: Table 9, pxxiii of the commentary
Note: The base case assumes an increase of **redacted** JointRep procedures per year.

The commentary considered that the use of real-world data provides greater certainty in the estimates than an epidemiological approach; however, there are several limitations: (i) the data supplied in the ADAR relate to utilisation from July 2019 to July 2020, which includes the period of disruption to elective surgery due to the COVID-19 pandemic; (ii) the 12-month period does not capture the impact of MSAC's negative advice in July 2020 regarding the comparative effectiveness and cost-effectiveness of BST-CarGel; (iii) historical utilisation may not match the population proposed in the ADAR; and (iv) it is unclear if the supplied data relate exclusively to use of JointRep in the private setting.

The commentary presented an alternative approach using Committee-In-Confidence PL billing data for JointRep (Billing Code DE681) and BST-CarGel (Billing Code SL072) forecast the financial implications of continued use of JointRep. **Redacted.**

14. Key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
Limited clinical evidence	One non-randomised study comparing JointRep+microfracture (MF) (n=46) with MF alone (n=23). Study is of very low quality with a critical risk of bias.
Claim of superior effectiveness against MF alone is uncertain	The claim of superior effectiveness is based on lower WOMAC scores in the JointRep arm (indicating improvement in knee pain and function). However, due to the very low quality of the study a claim of superior effectiveness is not supported.
Claim of non-inferior safety against MF alone is uncertain	No adverse events (AE) were reported in the JointRep study for either arm, raising concerns with the AE reporting methods and whether an assessment of comparative safety can be made.
Uncertainty in clinical evidence creates significant uncertainty in the economic model	Key issues include applicability of the JointRep study and the WOMAC instrument to the PICO population, and poor quality and reporting issues of the JointRep study. This translates into model uncertainty.
Economic model is rudimentary	Key model issues include: background mortality not related to interventions being modelled, alive state not distinguishing between degree of treatment success, three model cycles in the base case, questions regarding total knee arthroplasty (TKA)/reoperation, and limited usefulness of long-term extrapolation which assumes no QoL deterioration. MSAC to consider if this provides an adequate representation of the reality being modelled.
Comparison with BST-CarGel+MF is uninformative	No clinical claim for JointRep+MF *vs.* BST-Cargel+MF could be made based on the limited evidence. A naive indirect comparison was inappropriate due to systematic differences between studies and no verification of baselines between studies. In addition, the conversion of the WOMAC score for BST-CarGel+MF from VAS to the Likert scale was not validated and introduced further uncertainty in the cost-effectiveness comparison with BST-Cargel+MF. ESC considered there was limited usefulness of presenting a modelled ICER for JointRep+MF vs. BST-CarGel+MF.
Uncertainty in financial estimates	The estimated implications to the PL through continued listing of JointRep are highly uncertain. The predicted growth and utilisation (additional **redacted** procedures per year) was uncertain given the historical market growth observed for prostheses like JointRep. A major discrepancy in utilisation data, which provide the basis for financial projections, was identified between PL billing data and the applicant's sales data. The uncertainty for the MBS is regarding an unclear impact of JointRep on the uptake of the microfracture procedure.

ESC Discussion

ESC noted that JointRep is an arthroscopically injectable thermo-gel implant used in conjunction with microfracture. ESC noted that JointRep is currently listed on the Prostheses List (PL) and microfracture procedure (with or without JointRep) is claimed under existing

MBS items for arthroscopic surgery of the knee with chondroplasty (MBS item 49559, 49561 and 49562). ESC noted that PLAC is seeking advice from MSAC on the comparative safety, effectiveness and cost-effectiveness of JointRep plus microfracture compared with microfracture alone to inform PLAC consideration of whether JointRep should remain on the PL. ESC noted that in July 2020, MSAC considered a similar prosthesis (BST-CarGel, MSAC application 1569) and MSAC advised PLAC that BST-CarGel plus microfracture is not cost-effective as there was insufficient evidence to support non-inferior safety and superior effectiveness of BST-CarGel plus microfracture compared with microfracture alone.

ESC noted consultation feedback from the Australian Orthopaedic Association (AOA), which did not support the application as the AOA consider there is insufficient evidence of the benefit of JointRep with microfracture. From a consumer perspective, micofracture with or without JointRep requires extensive rehabilitation and multiple physiotherapy sessions, which exposes consumers to substantial out-of-pocket costs and access issues.

ESC noted the comparators (microfracture alone for population 1, lesions ≤2 cm^2; mosaicplasty, or microfracture in conjunction with BST-CarGel or Chondro-Gide for population 2, lesions >2 cm^2) and the clinical management algorithm.

ESC considered the clinical evidence, which consisted of one non-randomised study comparing JointRep plus microfracture (n=46) with microfracture alone (n=23) in patients with osteochondral defects (Grade III-IV) of the knee, with 12 and 24 month follow-up data (36 month unpublished). ESC noted the pre-ESC response indicating that 48 month follow-up data has been published[3] which reported that WOMAC[4] scores were maintained after 4 years (published in 2021 in an unranked journal). ESC noted that Populations 1 and 2 were not analysed separately. ESC considered that the quality of the JointRep study was poor, noting contradictory information including contradictory reporting of study design and data values between the two publications and unpublished study report. Further, the study was considered to have a critical risk of bias due to contrary descriptions of group allocation and claims that patients were matched by four variables, despite having a pool of only 69 patients. ESC also noted that an undisclosed number of study participants had osteoarthritis and a high proportion of patients were over 60 years of age, suggesting that cartilage defects were more likely to be chronic arthritis than acute cartilage injury.

Regarding the comparative effectiveness of JointRep plus microfracture versus microfracture alone, ESC noted the primary outcome measure in the JointRep study was the WOMACscore (pain, stiffness and physical function). ESC noted that while the WOMAC score was developed and validated for people with osteoarthritis of the hip or knee, ESC accepted the WOMAC score is an internationally recognised outcome measure. ESC noted that WOMAC scores were generally lower in the JointRep arm (indicating improvement in knee pain and function) but considered that conclusions could not be drawn due to the very low quality of the study. ESC considered that due to the insufficient quality of the JointRep study design, the claim of superior effectiveness of JointRep plus microfracture versus microfracture alone is uncertain.

Regarding the comparative safety of JointRep plus microfracture versus microfracture alone, ESC noted that no safety outcomes were reported in the JointRep study for both treatment arms, which contrasted to studies on BST-Cargel plus microfracture versus microfracture alone that reported adverse event (AE) in both study arms. ESC considered the lack of

[3] Indelli PF, et al. (2021) *Journal of Clinical Medical Research*. 2(1):1-13
[4] Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

adverse event (AE) reporting was likely due to issues with AE reporting methods. Thus, ESC considered that no meaningful comparison for safety was presented and that the claim of non-inferior safety compared with microfracture alone is uncertain.

Regarding the comparison of JointRep plus microfracture versus BST-Cargel plus microfracture, ESC noted the ADAR attempted to indirectly compare the results from the JointRep study with results from the two BST-Cargel studies. ESC noted there were differences in patient populations, the microfracture procedure and rehabilitation procedure, and that the divergence between the JointRep and BST-Cargel studies was unclear due to incomplete reporting in the JointRep study. ESC also noted that although studies on JointRep and BST-Cargel reported WOMAC scores, they used different WOMAC scoring methods and baseline WOMAC scores were not comparable. Overall, ESC considered that the indirect comparison of JointRep plus microfracture compared with BST-Cargel plus microfracture was inappropriate and not able to inform whether JointRep plus microfracture and BST-Cargel plus microfracture have a similar level of effectiveness.

ESC noted the cost-utility analysis comparing JointRep plus microfracture versus microfracture alone, and that issues with the quality of the clinical evidence flowed to the economic analysis. ESC noted that the health state utility values were derived from a transformation of WOMAC subscales and total score, and although the transformation methods were transparent and reasonable, the utility values were highly uncertain due to the poor quality of the clinical evidence. ESC also noted other translation issues including applicability issues between the JointRep study population and the patient population defined in the PICO. ESC noted costs were assumed to be identical for JointRep plus microfracture and microfracture alone, except for the cost of JointRep. ESC considered the long-term extrapolation assuming no deterioration in quality of life was of limited usefulness, and that questions remained regarding JointRep reoperation and total knee arthroplasty. ESC noted that MSAC may wish to consider if, in light of the above limitations, the analyses were adequate to inform its decision.

ESC noted the incremental cost-effectiveness ratio (ICER) for JointRep plus microfracture versus microfracture alone was $6,329 but the result was contingent on accepting the clinical claim, which had to take into consideration the poor quality of evidence and applicability concerns with the JointRep study. Other notable limitations of the model included that background mortality was not related to the interventions being modelled, the “alive” state did not distinguish between degree of treatment success, and there were only three cycles in the model’s base case. ESC noted the univariate sensitivity analyses presented in the ADAR and pre-ESC response, but considered that, given the poor quality of the evidence, changes in multiple parameters would be plausible. ESC noted that reducing all JointRep plus microfracture utilities by 20% increases the ICER to approximately $14,000, and reducing all JointRep plus microfracture utilities by 20% along with increasing microfracture alone utilities by 20% increases the ICER to approximately $61,000.

ESC also noted that the issues raised for the economic analysis comparing JointRep plus microfracture versus microfracture alone also apply to the cost-effectiveness analysis comparing JointRep plus microfracture against BST-CarGel plus microfracture. ESC noted the economic analysis appeared to take a cost-minimisation approach but without being supported by a claim of non-inferiority. ESC also noted the inconsistency between the claim that JointRep plus microfracture and BST-CarGel plus microfracture had similar effectiveness (noting there were no data to support this) and the incremental effectiveness of JointRep plus microfracture compared with BST-CarGel plus microfracture of 0.2 QALYs.

In addition, ESC noted that the conversion of the WOMAC score for BST-Cargel plus microfracture from VAS[5] to Likert scale was not based on a validated approach, which added an additional element of uncertainty to the cost-effectiveness analysis against BST-CarGel plus microfracture. Overall, ESC considered there was limited usefulness of presenting a modelled ICER for JointRep plus microfracture versus BST-CarGel plus microfracture.

ESC noted the ADAR forecast the financial implications of continued use of JointRep via the MBS and the PL. ESC noted that the financial impact to the PL through continued listing of JointRep could vary from $5,203,008 - $6,070,176 in Year 1 and rising to $6,720,522 - $7,804,512 in Year 5. ESC noted a considerable discrepancy in the utilisation estimates when based on PL billing data versus the applicant's sales data. The reason for this discrepancy was unclear, and ESC queried if it could be partly explained by inaccurate billing records in the private setting. ESC was also uncertain whether the historical sales data align with the proposed population. ESC also noted, given the market growth observed for a prostheses like JointRep, the predicted growth and utilisation (additional **redacted** procedures per year) was uncertain. ESC considered it was plausible that JointRep had increased the use of microfracture, if patients/clinicians were previously hesitant to undergo treatment with microfracture alone due to the prolonged post-procedure period without weight bearing.

ESC noted the pre-ESC response reported that an international (Australian/Canadian/New Zealand) multicentre randomised clinical trial[6] (n=185, randomised 2:1) is due to commence June 2021 to assess the effectiveness and safety of JointRep plus microfracture versus microfracture alone when treating symptomatic focal articular cartilage lesions in the knee (femoral condyles or trochlea) with trial results expected December 2025. The applicant has proposed that JointRep remain on the PL at a **redacted** benefit ($**redacted**) until the upcoming clinical trial is complete. ESC also noted the applicant provided additional multivariate sensitivity analyses exploring the **redacted** PL benefit and arbitrary reductions in incremental QALY benefit, but queried whether **redacted** the PL benefit can offset the uncertainty in the clinical evidence.

15. Other significant factors

Nil

16. Applicant comments on MSAC's Public Summary Document

The applicant would like to thank MSAC and the Secretariat for all its work in considering this application and will take note of its advice in any further submission. We are, however, very concerned at MSAC's contention that a trial of microfracture versus placebo be necessary for any future application to be successful. The applicant has consulted with an independent Clinical Research Organisation and a number of Orthopaedic surgeons taking part in the current JMAC study and have been advised there are likely to be considerable barriers in gaining ethics approval for a trial of this nature.

[5] Visual analogue scale

[6] A Comparison of JointRep™ and Microfracture in Repair of Cartilage Lesions on the Femoral Condyle or Trochlea (JMAC) – NCTC 04840147
https://clinicaltrials.gov/ct2/show/NCT04840147?term=JointRep&draw=2&rank=1

17. Further information on MSAC

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