



Australian Government
Department of Health

RATIFIED PICO

Application 1578:

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

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

Component	Description
Patients	<p>Patients undergoing microfracture for repair of 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.</p> <p>Within this population, there are two sub-populations of interest:</p> <ol style="list-style-type: none"> 1. Patients with a defect $\leq 2 \text{ cm}^2$ in size 2. Patients with a defect $> 2 \text{ cm}^2$ in size
Intervention	<p>JointRep™ (Oligo Medic, Quebec, Canada) is to be used in conjunction with microfracture of the knee. A procedure already listed on the Medicare Benefits Schedule (MBS) (items 49559, 49561 and 49562).</p>
Comparator	<p>For sub-population 1, patients with defects $\leq 2 \text{ cm}^2$, the comparator procedure for microfracture with JointRep™ is:</p> <ul style="list-style-type: none"> • Microfracture alone, in conjunction with standard of care <p>For sub-population 2, patients with defects $> 2 \text{ cm}^2$, the appropriate comparators include:</p> <ul style="list-style-type: none"> • Microfracture alone, in conjunction with standard of care • Other scaffold products available in Australia (e.g. BST-Cargel® and Chondro-Gide®) used in conjunction with microfracture. • Mosaicplasty <p><i>While the comparators for this application (1578) and similar current application 1569 should be as consistent as possible, there are slight differences for larger lesions (sub-population 2) in this application (1578).</i></p> <p><i>In addition, MACI/ACI were initially proposed as comparators, but PASC confirmed MACI/ACI are not comparators for the product in this application 1578 (or the product in similar application 1569). However, the assessment reports for application 1578 (and similar application 1569) should clearly detail the evidence (or lack thereof) for MACI/ACI against the product in application 1578 (and similar product in application 1569). This is for completeness, and to ensure robust information is available if MSAC wants to consider it.</i></p>
Outcomes	<p><i>Patient-relevant</i></p> <ul style="list-style-type: none"> • Safety: Any adverse events associated with JointRep™ or comparators • Effectiveness: Primary outcomes include pain and joint function, activity rating, health-related quality of life, time to weight bearing and OMERACT (Outcome Measures in Rheumatology). Secondary outcomes include macroscopic assessment of cartilage repair, range of motion, degree of joint effusion and locking or catching sensations.

Component	Description
	<p data-bbox="448 181 671 215"><i>Healthcare system</i></p> <ul data-bbox="499 226 1362 383" style="list-style-type: none"> <li data-bbox="499 226 1362 259">• Cost of acquiring JointRep™, its implantation and cost of its disposal <li data-bbox="499 266 1086 300">• Cost of comparator products and procedures <li data-bbox="499 306 1257 340">• Cost of associated services, such as diagnosis and follow-up <li data-bbox="499 347 1062 383">• Rehabilitation costs, such as physiotherapy

PICO or PPICO rationale for therapeutic and investigative medical services only

Note: This is an application to inform the listing of a product on the Prostheses List. If the product is recommended by MSAC (and approved by PLAC), an existing MBS item may be used to implant the product, with or without an amendment to the item descriptor, or a new MBS item will be created for delivery of the product.

This product will be used in conjunction with microfracture, a procedure for which MBS items and funding already exist (the applicant nominated MBS items 49559 and 49562). Descriptors for these MBS items are provided in the section of this document titled 'Proposed Item Descriptor'.

Population

PASC supported the two sub-populations defined in the Draft PICO, based on discussion about the comparator.

PASC confirmed that populations in the PICO should be checked for alignment with existing MBS items, and they must reflect the ARTG listing (presented later in this document). In summary, the populations should specify how the grade III and IV defects are classified; explicitly state microfracture; and explicitly exclude degeneration (e.g. osteoarthritis).

PASC noted the osteochondral defect would be a discrete lesion.

PASC noted uncertainty associated with estimating the number of microfracture procedures (provided in conjunction with JointRep) on the Australian MBS each year (e.g. MBS item 49561 had ~30,000 procedures claimed in 2017-18).

PASC acknowledged that utilisation estimates may be larger than predicted in this PICO, because microfracture may also be claimed under other MBS items.

Clinical expert advice was that MBS item 49562 is the most likely item to be billed for microfracture. In the 2017/18 financial year, a total of 3,207 procedures were claimed under item 49562. Microfracture may also be being billed under MBS item 49559, for which there were 74 claims processed in the 2018/19 financial year.

PASC advised that consistency should be applied between this application (1578) and similar current application 1569.

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.

The applicant advised that only one unit of JointRep™ is needed, regardless of the number of lesions.

Within the population, there are two sub-populations for whom treatment is different depending on their defect size:

1. Patients with a defect $\leq 2 \text{ cm}^2$ in size
2. Patients with a defect $> 2 \text{ cm}^2$ in size

While clear size parameters assist the evaluation stage, the applicant cautioned that, in practice, it is largely a matter of clinical discretion. The applicant cautioned there may be significant crossover between the two groups, which should be taken into account throughout the assessment. The applicant recommended other clinical papers be referenced, which suggest other cut-off points for the use of microfracture.

Articular, or hyaline cartilage, is a smooth white tissue that covers the ends of bones where they come to form joints. Its function is to enable bones to glide over one another with little friction. It is composed of an extracellular matrix (ECM) consisting of water, collagen and proteoglycans as well as specialised cells called chondrocytes which are responsible for the development, maintenance and repair of the ECM. Articular cartilage is devoid of blood vessels, lymphatics or nerves.^{1,2}

Damage to articular cartilage, caused by trauma, such as a sporting injury, or normal wear and tear, can result in pain and stiffness if the joint surface is no longer smooth, as the bones no longer glide easily over one another without friction. It can also lead to arthritis in the joint.² Cartilage defects are graded using either the Outerbridge Arthroscopic Grading System (Table 1) or the ICRS Grading System (Table 2). The population, as specified by the applicant (Application Form, page 14) is patients with Grade III or IV lesions (Outerbridge grading system). Grade III is characterised by having deep lesions but without exposed bone, while Grade IV lesions are those that extend through to the subchondral bone. However, a clinical expert advised that microfracture is not indicated for lesions with significant bone damage or loss.³ In addition, they stated that the presence of osteoarthritic damage to the knee and knee malalignment are usually contraindications for microfracture.³

Table 1 Outerbridge Arthroscopic Grading System⁴

Grade 0	Normal cartilage
Grade I	Softening and swelling
Grade II	Superficial fissures
Grade III	Deep fissures, without exposed bone
Grade IV	Exposed subchondral bone

Table 2 International Cartilage Repair Society Grading System⁴

Grade 0	Normal cartilage
Grade 1	Nearly normal (superficial lesions)
Grade 2	Abnormal (lesions extend <50% of cartilage depth)
Grade 3	Severely abnormal (>50% of cartilage depth)
Grade 4	Severely abnormal (through the subchondral bone)

Owing to a lack of blood vessels, and low potential of chondrocytes to replicate, articular cartilage has limited ability to self-heal if damaged. Microfracture is one of several surgical procedures used to repair defects of articular cartilage. The aim of microfracture is to stimulate the growth of new articular cartilage by creating blood flow to the damaged area. This is done by making multiple holes in the subchondral bone that lies underneath the cartilage, through to the more vascular bone using a tool called an awl. The resulting flow of blood creates a clot in the chondral defect, recruiting mesenchymal stem cells to heal it into a fibrocartilaginous scar.¹

Clinical expert advice was that microfracture is only suitable for small damaged areas (usually lesions $\leq 2 \text{ cm}^2$ in size).^{3,5} There are no restrictions on patient age or weight associated with the MBS item used for microfracture. However, the ICRS note that in general, poorer microfracture results are seen in older and overweight patients.⁵ In addition, a clinical expert stated that microfracture treatment is uncommon in patients over 55 years and that caution should be used in patients with a body mass index over 40.³ Consistent with this advice; the Application Form stated that JointRep™ should not be used for generalised degeneration, meniscal deficiency or established osteoarthritis.⁶

While age was a factor in trial data (patients aged 15 - 55 years), PASC advised there is no reason to impose an upper age limit of 55, given many people in their 60s and 70s are active and would benefit from this procedure. PASC acknowledged MSAC may choose to impose age limits in the MBS item descriptor. The applicant advised that, in Australia, it is unusual for surgeons to use microfracture or other bone marrow stimulation techniques for osteoarthritis or in older populations. However, they clarified it may be appropriate for carefully selected patients.

Clinical expert feedback about follow-up after microfracture was that patients should see their surgeon at 2, 6 and 12 weeks post procedure, and then at 12 months with a repeat magnetic resonance imaging (MRI) scan of the lesion at 6 or 12 months.³ They also advised that physiotherapy is required to protect the joint by strengthening and toning the muscles around it.³ The importance of physiotherapy is also expressed by the ICRS. The ICRS further state that weight bearing on the affected joint should be minimised for around eight weeks following surgery to ensure proper function is restored.⁵

Rationale

In the pivotal study on JointRep™ by Pipino et al (2019)⁷, the patient description is as follows:

“Patients affected by moderated to severe (Outerbridge III-IV) osteochondral lesions in the knee secondary to primary osteoarthritis or trauma and refractory to conservative measures were included in the study. Patients with associated conditions such as previous partial meniscectomy, cruciate ligament lesions, or failed microfracture surgery (only in one case) were also included in the study and associated procedures were performed simultaneously and in addition to the surgical treatment of the chondropathy.”

The population included in this study is different to the population suggested by PASC, in that the population suggested by PASC does not include lesions secondary to primary osteoarthritis, nor does it separate the analyses of lesions based on their size.

PASC advised that, while a body mass index (BMI) limit is unlikely to be needed, it noted the suggested BMI limit in application 1578 (40 kg/m^2) was different to that referenced in similar (but different product) application 1569 (BMI reference of 30 kg/m^2).

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

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

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

Intervention

JointRep™ is a polyglucosamine/glucosamine carbonate based hydrogel that, when applied directly onto cartilage lesions prepared using microfracture, provides a scaffold for chondrocyte cells, thereby assisting with cartilage repair.⁸

PASC noted the application for JointRep is for the knee, but noted the product is also used in other parts of the body. PASC noted there are ongoing international clinical studies for JointRep, but these relate to the ankle and hip.

According to Ortho BioMedica, JointRep™ comes as a three-part liquid formulation consisting of a gel of sterile water for injection, poly-N-acetyl-D glucosamine and carbonated glucosamine. The three solutions are mixed together in a 4 mL syringe for arthroscopic administration, a process taking less than 2 minutes to complete. Following injection the solution solidifies into a gel within one minute, in response to body temperature and pH.⁹ Ortho BioMedica state that the gel remains in place for up to three to four months whereby it then breaks down and is absorbed by the body. Ortho BioMedica further state that preparation and implantation of JointRep™ takes three to five minutes to complete.⁹ It is purported by the applicant (Application Form, page 17) that JointRep™ allows immediate weight bearing compared with the traditional six- to eight week non-weight bearing period associated with microfracture alone.

The applicant advised that delivery of the intervention is by an orthopaedic surgeon performing the microfracture procedure (Application Form, page 15). The additional procedure time required to administer the intervention is reportedly negligible (Application Form, page 22). No specific training is required to use JointRep™ (Application Form, page 16).

Clinical expert advice was that microfracture is usually performed arthroscopically, as a day procedure.³ Three types of anaesthesia may be used for the microfracture procedure - local, spinal or general, depending on the patient.¹⁰ The applicant stated the procedure is usually performed under general anaesthesia. The clinical expert noted the addition of JointRep™ is unlikely to affect any of these factors.³

No specific physiotherapy regime following the use of JointRep™ could be identified. Clinical expert advice was that use of JointRep™ is unlikely to change follow-up requirements post-microfracture (as described in the Population Section of the PICO).³ In the Application Form (page 17), the applicant stated that “Patients treated with microfracture and JointRep™ will require an intensive rehabilitation program. This is required so the complex musculature supporting the knee is strengthened, the patella-femoral alignment is correct (so a mal-tracking patella is avoided), and the patient has sufficient endurance to return to normal activities.” Product-specific ‘Knee Physiotherapy Guidelines’ provided by the applicant state that a 12 to 14 week formal physiotherapy program is advised as a minimum, with two to three sessions per week and daily in-home exercises. The applicant advised these are conservative guidelines, with a more aggressive program being undertaken by many patients, particularly younger people and athletes.

The applicant advised that individual surgeon physiotherapy/rehabilitation recommendations can be variable.

The applicant stated that, should the repair fail or symptoms recur, a second surgical repair may be attempted, with a similar knee rehabilitation program (Application Form, page 17).

JointRep™ is listed on the Australian Register of Therapeutic Goods (ARTG) (ARTG number 316444). The intended purpose provided on the ARTG for JointRep™ (in their public summary document) is as follows:

“JointRep™ injectable implant is indicated for 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.”⁶

Feedback from the applicant, received during preparation of this PICO, was that “Clinical evidence suggests that JointRep™ is effective for lesions larger than 2 cm² and will likely be reserved for use in this patient group.” The applicant further noted that “Patients with large lesions are an underserved population, with few available interventions other than joint arthroplasty”.

Rationale

JointRep™ can be used in joints other than the knee. The applicant has noted clinical trials (not yet completed) where JointRep™ is being evaluated in osteochondral lesions of the talus and the metatarsal phalangeal joint (Application Form, pages 8 and 9). In addition, a website by Ortho Biomedica states “JointRep™ can be applied to lesions of any size or shape in any joint including the knee, hip, elbow, ankle and wrist. Multiple lesions can be treated in the same procedure.”¹¹ Therefore, should the product be listed on the Prosthesis List it may be necessary to specify the particular population in whom usage is indicated (anatomical location, lesion size, other patient characteristics).

When considering the above, PASC may wish to take into account that comparator product BST-Cargel is listed on the Department of Health’s Prosthesis List with no apparent restrictions in its description except that it is used on a debrided cartilage lesion that has been surgically prepared with microfracture.

Comparator

PASC noted the PICO has stratified the populations based on defect size of 2 cm², which is based on the effectiveness of microfracture, not JointRep. However, PASC noted that, while there is a commonly held clinical view that microfracture alone is not effective for defects >2 cm, it was difficult to find literature that supports this.

PASC questioned whether there should be different comparators for different defect sizes, even though this is not the case in the pivotal study (Pipino et al. 2019), nor is defect size specified in the ARTG listing for the proposed intervention. It was noted there are no clinical practice guidelines in Australia, and this lack of consistency is reflected in the PICO and policy documents.

PASC agreed that, for defects ≤2 cm² (sub-population 1), microfracture alone is the comparator.

PASC advised that, while comparators for this application (1578) and similar current application 1569 should be as consistent as possible, for larger defects (sub-population 2 in application 1578), the comparators should be microfracture, plus other options available. PASC clarified and acknowledged it is not useful to assess comparators not in use in Australia.

In line with similar current application 1569 (different product and applicant), the intervention would only be used in patients with larger lesions of > 2 cm² (sub-population 2) if these patients have an intact subchondral endplate. Patients with larger lesions who do not have an intact subchondral endplate are indicated for joint replacement. PASC therefore agreed the comparator for sub-population 2 should include microfracture.

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

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

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

Since the PASC meeting, the Department advised that, while mosaicplasty, other scaffold products available in Australia, ACI and MACI are not comparators for population 2 of similar current application 1569, mosaicplasty and other scaffold products (but not ACI/MACI) are comparators for sub-population 2 of this application (1578).

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

At the PASC meeting, clinical advice was that mosaicplasty is rarely used in Australia, because it is a technically difficult procedure to perform, and it may not be a suitable comparator for sub-population 2.

Sub-population 1 (patients with a defect $\leq 2 \text{ cm}^2$ in size)

The comparator procedure nominated by the applicant (Application Form, page 17) is microfracture, without the addition of JointRep™.

Sub-population 2 (patients with a defect $> 2 \text{ cm}^2$ in size)

Based on discussions with a clinical expert³, BST-Cargel and Chondro-Gide® (other bioscaffold products used in conjunction with microfracture to assist with cartilage repair), as well as other marrow stimulating techniques (subchondral drilling, abrasion arthroplasty and nanofracture) should be considered comparators.

These are referred to as autologous matrix-induced chondrogenesis (AMIC) procedures.¹² The applicant confirmed that, while all these procedures are designed to disrupt the cortical surface of the underlying bone (and therefore may be considered variations of microfracture), JointRep can be used in conjunction with all of them, based on the principle of improving bone marrow stimulation procedure outcomes.

In addition, mosaicplasty, a procedure claimed under MBS item 49563, was also considered a comparator for sub-population 2 in this application (1578), but not for similar current application 1569.

In the financial year 2018 to 2019, a total of 1,980 procedures were claimed under MBS item 49563. However, it should be noted not all procedures claimed under this item would be for mosaicplasty, so the true number of mosaicplasty procedures performed during this time would be lower than this.

1. BST-Cargel® (Smith and Nephew, London, UK)

BST-Cargel® is a chitosan-based (derived from the exoskeleton of crustaceans) liquid bioscaffold alleged to assist in cartilage repair. It is a single-stage procedure with five key steps¹³:

1. The defect is exposed arthroscopically and protruding synovial tissue removed.
2. The damaged cartilage is debrided down to the subchondral bone.
3. The defect is arranged in a horizontal position and the arthroscopy liquid is drained.
4. The BST-Cargel® is injected and the entire defect filled, forming a stable clot after 15 minutes.
5. Intra-articular drainage is inserted, and the arthroscopy portals closed.

BST-Cargel® is prepared by combining the chitosan solution with a buffer, leaving the solution undisturbed for a minimum of 10 minutes and then slowing mixing it with 4.5 mL of fresh autologous blood. The solution is then shaken vigorously for 10 seconds, after which 4 to 6 mL of the BST-Cargel®/blood mixture is drawn into a syringe and then administered in a drop-wise manner over the debrided cartilage lesion, which has previously been prepared through bone marrow stimulation.¹³

14

BST-Cargel® reportedly works by:

- physically stabilising the blood clot;
- impeding the retraction of the clot and maintaining critical blood components above the marrow holes and thus enhancing repair;
- providing a structural framework for cellular growth; and,
- generating an adhesive bond between the clot and surrounding cartilage.¹⁵

Thus, it is said to achieve better healing than could be achieved with bone marrow stimulation alone by improving the quantity of the blood clot present in the cartilage lesion; this being the critical factor for bone marrow-derived cartilage repair.^{14, 16}

BST-Cargel® is listed on the Prosthesis List (Billing Code SL072) and ARTG. (ARTG number 252732). Its intended purpose as listed on the ARTG is as follows:

“BST-Cargel® is a medical device intended to promote hyaline cartilage regeneration when used in conjunction with the bone marrow stimulation technique for repair of focal articular cartilage lesions. Treatment with BST-Cargel® should be performed by an orthopaedic surgeon”¹⁷

As defined in its listing on the ARTG, BST-Cargel® can be used with any bone marrow stimulating technique, not just microfracture.

Treatment with BST-Cargel® is administered by an orthopaedic surgeon and is administered through either a mini-arthrotomy or by arthroscopy.¹⁵

A summary of the recommended physiotherapy program following treatment with BST-Cargel® is described in a product brochure on BST-Cargel® by Piramal Life Sciences (Canada). The details are as follows:

- Standard knee immobiliser for the first 24 hours, and thereafter for 14 days at night and during all movement
- Non-weight bearing on the treated knee for 6 to 8 weeks
- Frequent physiotherapy for 12 weeks, using typical modalities for joint health
- No high impact activities requiring jumping or pivoting for 12 months.¹⁴

2. Chondro-Gide® (Geistlich Pharma AG, Wolhusen, Switzerland)

Please note that the applicant advised that Chondro-Gide® is used rarely, if ever, in Australia

Chondro-Gide® is a bilayer collagen Type I/III matrix used for the treatment of cartilage defects.¹⁸ It is produced from porcine collagen and is naturally resorbed.¹⁹

Following microfracture, Chondro-Gide® is used to cover the cartilage defect. The porous layer of the Chondro-Gide® matrix, which is composed of collagen, is purported to support cell invasion and attachment while the compact layer is said to prevent the mesenchymal stem cells from diffusing into the joint space.

Chondro-Gide® is available in three different product sizes that can be cut into shape to enable treatment of different sized cartilage defects. The smaller size (20 x 30 mm) is recommended for use in the repair of smaller chondral and osteochondral lesions of the talus, knee and hip using either AMIC or ACI. The medium size (30 x 40 mm) is recommended for cartilage lesions in the knee or hip with AMIC, while the largest size (40 x 50 mm) is recommended for large cartilage defects of the knee using ACI.²⁰ For use with AMIC procedures on the knee, Chondro-Gide is indicated for focal chondral and osteochondral lesions (Grade III-IV using Outerbridge Classification) ranging in size from 2.0 to 8.0 cm².¹⁹

The product is prepared by making an imprint of the defect using an aluminium template which is then cut out and transferred onto the Chondro-Gide®. The side of the template facing the defect is transferred onto the smooth surface of the matrix. Fixation of Chondro-Gide® to the defect (porous layer facing the bone surface) is achieved by either a commercially available fibrin glue or sutures. The fibrin glue is said to take approximately five minutes to set.¹⁹

Physiotherapy including isometric muscle activation and closed kinetic chain exercises are recommended as part of the postoperative care, although the duration and frequency are not reported. Patients are on crutches for the first six weeks following surgery.¹⁹

Chondro-Gide® is listed on the ARTG (ARTG number 146887) but is not listed on the Prosthesis List. Its intended purpose as listed on the ARTG is as follows:

“Chondro-Gide is an orthopaedic cartilage repair membrane used to cover articular cartilage defects treated with autologous chondrocyte transplantation or bone marrow stimulation techniques.”²¹

3. Mosaicplasty

Mosaicplasty involves harvesting cylindrical plugs of bone and cartilage taken from less weight bearing areas of the patient’s knee and then transferring them into tunnels that have been drilled into the defective section of cartilage. The donor site is left to heal naturally, with the tunnels becoming filled with cancellous bone covered in a surface of fibrocartilage. It is termed mosaicplasty as the grafts are implanted in a mosaic-like fashion²²

As for microfracture, the procedure is typically done as an outpatient procedure, with the patient able to go home the same day.²² Following surgery patients can start walking immediately with crutches (no weight bearing). Partial weight bearing can occur at two to four weeks following surgery and full weight bearing at three to five weeks.²²

Rehabilitation following mosaicplasty is similar to microfracture and is likely to vary more between individual surgeons than the techniques themselves.²³

Rationale

There are no limitations on the provider or setting in which the comparator procedures can be provided.

Outcomes

PASC confirmed the existing outcomes in Draft PICO 1578, and recommended adding the following to the list of effectiveness outcomes:

- time to weight bearing; and
- OMERACT (Outcome Measures in Rheumatology), as a standardised measure.

The applicant questioned whether OMERACT was an appropriate outcome measure, stating it is unlikely this instrument was used in any relevant trials. Given the applicant's preference of WOMAC and other instruments are included below, the addition of OMERACT should do no harm.

PASC advised that follow-up care costs should be included under rehabilitation costs (e.g. physiotherapy).

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

Patient-relevant outcomes

The outcomes suggested by the applicant (Application Form, page 19) are serious adverse events, and Western Ontario and McMaster Universities Index (WOMAC) scores. Other recommended outcomes that should be included in any assessment of JointRep™ are provided below.

Safety

- Any serious adverse events associated with the intervention or the comparators.
- Any treatment or device-related adverse events (including: joint effusion, joint swelling, haematoma, muscle vein thrombosis, muscle hypertrophy, headache, wound infection, arthralgia, nausea, deep vein thrombosis, pulmonary embolism).

Clinical effectiveness

Guidelines for the design and conduct of clinical studies in knee articular cartilage repair have been produced by the ICRS.^{24, 25} Primary and secondary effectiveness endpoints deemed relevant by the ICRS for cartilage repair studies and the associated tools for their measurement are as follows:

Primary endpoints:

- Pain and joint function (measured using any of the following: the Knee injury and Osteoarthritis Outcome Score (KOOS), International Knee Documentation Committee (IKDC) Subjective Knee Form, Western Ontario McMaster Universities Osteoarthritis Index (WOMAC), Modified Cincinnati Knee Rating System, Short Form 36 Health Survey (SF-36) and the Lysholm scoring scale)
- Activity rating measured using either the Tegner-Wallgren Activity Scale or the Marx Activity Rating Scale
- Health-related quality of life (measured using any of the following: SF-36, SF-12 and EQ-5D).
- Time to return to work and return to normal activity
- Subsequent surgical procedures (e.g. knee arthroplasty, revision chondroplasty)
- Long term (5 year) function, pain and activity outcomes should also be included
- Time to weight bearing
- OMERACT (Outcome Measures in Rheumatology)

Secondary endpoints:

- Macroscopic assessment of cartilage repair (measured by the ICRS and Oswestry macroscopic cartilage evaluation scores)
- Range of motion
- Degree of joint effusion
- Locking or catching sensations
- Articular cartilage repair structure analysis (as assessed using cartilage-specific magnetic resonance imaging sequences and the magnetic resonance observation of cartilage repair tissues (MOCART) scoring system)
- Histological evaluation (assessed using the ICRS I and ICRS II scoring systems)

Healthcare system outcomes

- All resource use associated with the intervention including the cost of the JointRep™
- All resource use associated with the comparator
- Costs associated with diagnosis and follow-up
- Rehabilitation costs (e.g. physiotherapy)

The proposed intervention is expected to have minimal impact on healthcare system resource utilisation. According to the manufacturer, JointRep™ is administered in a one-step procedure as part of a standard arthroscopy with preparation and implantation taking only 3 -5 minutes.⁹ The only expected impact is in relation to the cost of the product and its disposal.

The applicant has provided the following healthcare system cost evaluations for JointRep™ (Table 3 and

Table 4) (source: Application Form pages 21 and 22).

Table 3 Utilisation projections of JointRep™ provided by Applicant (Application Form, page 21)

	Description	Source	2021	2022	2023
A	Eligible Population	Assuming 1.6% population growth and static PHI (private health insurance) membership rates, with an eligible population of 3,333 in 2020 (based on utilisation of MBS items 49559 and 49562)	3,386	3,440	3,493
B	Percentage of Eligible Population (Uptake Rate)	Assuming additional 5.0% of population each year	14.1%	19.1%	24.1%
C	Number of Microfracture and JointRep™ Procedures	A*B	477	657	841

Table 4 Summary of expected costs of JointRep™, provided by Applicant (Application Form, page 21)

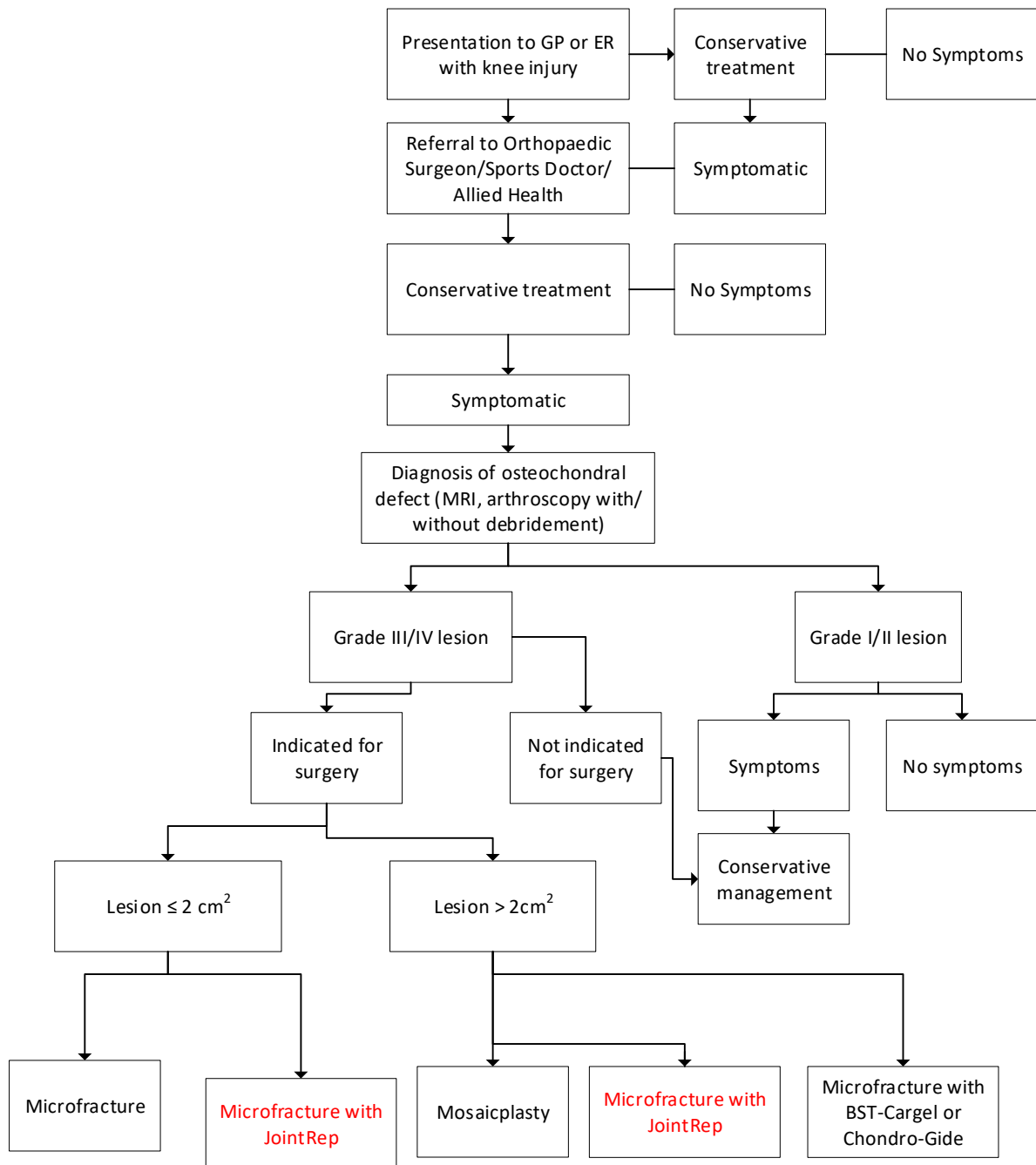
Service	Item	Fee/Cost	Medicare Benefit	PHI Benefit	Cost
Anaesthesia	MBS 17610	\$43.00	\$32.25	\$10.75	\$43.00
	MBS 21382	\$79.20	\$59.40	\$19.80	\$79.20
	MBS 23063	\$118.80	\$89.10	\$29.70	\$118.80
Microfracture Procedure	MBS 49562	\$735.50	\$551.65	\$183.85	\$735.50
Assistant	MBS 51303	\$147.10	\$110.35	\$36.75	\$147.10
Hospital	Assume AR-DRG I24B (minus medical costs)	\$,3148.00		\$3,148.00	\$3,148.00
JointRep™	PL Rebate	\$6,022		\$6,022	\$6,022
Total			\$842.75	\$9,450.85	\$10,293.60

Proposed clinical management algorithm for identified population suggested by assessment group

PASC advised that the algorithm provided by the assessment group was more appropriate than the one provided by the applicant, because it stratified by size. However, PASC noted the algorithm needed further modification, to reflect the correct comparators (i.e. microfracture alone for the smaller lesion group in this application [1578]; and microfracture + other products for the larger lesion group in this application). This is reflected in the algorithm directly below.

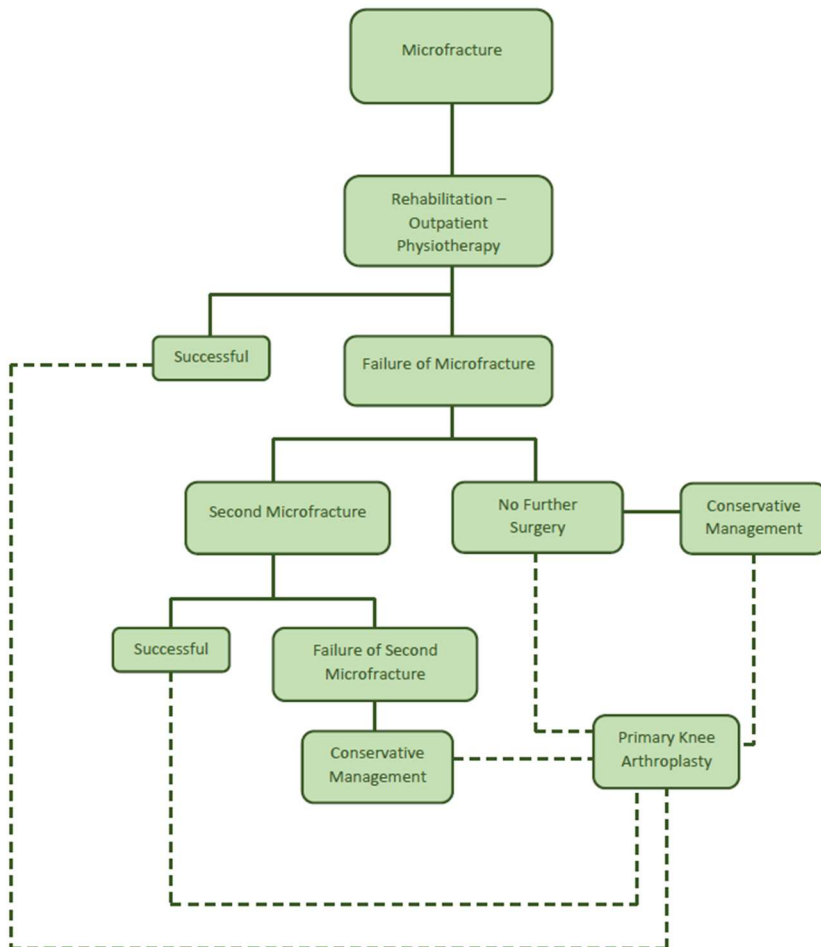
PASC advised the algorithms for application 1569 (and similar current application 1578) should be consistent as far as possible (acknowledging the algorithms for larger lesions will be different).

The applicant claims the clinical pathways do not adequately capture/communicate that patients with larger lesions are an under-served population, with few available interventions, other than joint arthroplasty.



Abbreviations: ACI = autologous chondrocyte implantation; ER = emergency room; GP = general practitioner; MRI = magnetic resonance imaging; OATS = osteochondral autograft transfer.
 The proposed intervention is indicated in red.

Clinical Pathway following Microfracture



Proposed economic evaluation

PASC confirmed that, for the smaller defect size, a cost-utility or cost-effectiveness analysis would be appropriate, because of the superiority claim over microfracture alone.

PASC noted that no specific claim was included in the application for comparisons between JointRep™ and BST-Cargel®, or JointRep™ and Chondro-Gide®.

It is likely the claim for these comparisons is one of non-inferiority, so a cost-minimisation analysis is appropriate. However, PASC noted there was a presumption of superiority to BST-Cargel®, because of reduced time to weight bearing.

PASC advised that, if different comparators are to be used for larger defects, the effectiveness claims will need to be defined for each.

Sub-population 1 (patients with a defect ≤ 2 cm² in size)

The applicant has claimed microfracture with JointRep is superior to microfracture alone based on outcomes reported in the pivotal trial Pipino et al. (2019) who reported use of JointRep improved WOMAC score compared to microfracture alone.⁷

On the basis of this claim, a cost utility or cost effectiveness evaluation is appropriate.

Sub-population 2 (patients with a defect > 2 cm² in size)

No specific claim for the comparison between JointRep™ and BST-Cargel® or JointRep™ and Chondro-Gide® was included in the Application. However, PASC noted there was a presumption of superiority to BST-Cargel®, because of reduced time to weight bearing. In that case, a cost-utility analysis would be appropriate.

Proposed item descriptor (via amendment to existing MBS items)

No new MBS funding is sought for this application; if the treatment is assessed as safe, clinically effective and cost effective, it would be used under existing MBS items for microfracture (see below). As such, a proposed item descriptor was not provided by the applicant.

If the treatment is supported by MSAC, these existing items would be left unamended; be amended to reflect the new implant; or perhaps a new item would be listed (to cover existing service, but under its own item number).

PASC noted that, once PLAC has considered MSAC's advice on application 1578, all content/contraindications/exclusion criteria relating to the implant should be captured within existing MBS items relevant to microfracture (e.g. items 49559, 49561 and 49562).

Existing MBS item 49559

KNEE, arthroscopic surgery of, involving chondroplasty requiring multiple drilling or carbon fibre (or similar implant; including any associated debridement or osteoplasty – not associated with any other arthroscopic procedure of the knee region.

Existing MBS item 49562

KNEE, arthroscopic surgery of, involving 1 or more of: partial or total meniscectomy, removal of loose body or lateral release; where the procedure includes chondroplasty requiring multiple drilling or carbon fibre (or similar) implant and associated debridement or osteoplasty – not associated with any other arthroscopic procedure of the knee region

Existing MBS item 49561

KNEE, arthroscopic surgery of, involving 1 or more of: partial or total meniscectomy, removal of loose body or lateral release; where the procedure includes associated debridement, osteoplasty or chondroplasty – not associated with any other arthroscopic procedure of the knee region.

Consultation feedback

PASC noted that one piece of feedback was received from a peak medical professional organisation, which was not supportive of the intervention because:

- the evidence of benefit was not convincing
- other treatments are more effective
- the cost is high
- there is probability of leakage.

The feedback suggested other comparators and recommended the need for longer-term outcome studies on microfracture.

Other issues

There is potential for out-of-pocket expenses with JointRep™, as well as issues regarding equity and access. These should be addressed during the assessment phase.

Next steps

Once PICO 1578 is ratified, the application can PROCEED to the pre-Evaluation Sub-Committee (ESC) stage. The applicant is yet to decide if it will prepare its own ADAR (applicant-developed assessment report) OR will ask the Department to arrange a DCAR (Department-contracted assessment report).

For consistency, the Department should ensure that the HTA group that prepares DCAR 1578 (or the Commentary of ADAR 1578 [formerly known as a Critique] is the same HTA group that prepares the Commentary of ADAR 1569 (noting that applicants for 1578 and 1569 are different, and it is the applicant's choice to prepare their own ADAR or ask the Department to contract a DCAR).

References

1. Sophia Fox, A. J., Bedi, A. & Rodeo, S. A. (2009). 'The basic science of articular cartilage: structure, composition, and function'. *Sports health*, 1 (6), 461-8.
2. Surgeons, A. A. o. O. (2009). *Articular Cartilage Restoration*. [Internet]. American Academy of Orthopaedic Surgeons. Available from: <https://orthoinfo.aaos.org/en/treatment/articular-cartilage-restoration/> [Accessed 18th June 2019].
3. Expert orthopaedic surgeon. Personal communication (via phone conversation on 17/6/2019). 2019.
4. Watts, E. & McCulloch, P. (2018). *Articular Cartilage Defects of Knee*. Available from: <https://www.orthobullets.com/knee-and-sports/3133/articular-cartilage-defects-of-knee> [Accessed 1st July 2019].
5. International Cartilage Regeneration and Joint Preservation Society (?). *Debridement and microfracture*. [Internet]. International Cartilage Regeneration and Joint Preservation Society. Available from: <https://cartilage.org/patient/about-cartilage/cartilage-repair/debridement-and-microfracture/> [Accessed 1st July 2019].
6. Australian Government Department of Health (2019). *Public Summary for ARTG Entry 316444. Device Technologies Australia Pty Ltd - JointRep- Cartilage biomatrix implant*. [Internet]. Australian Government Department of Health. Therapeutic Goods Administration. Available from: [https://www.ebs.tga.gov.au/servlet/xmlmillr6?dbid=ebs/PublicHTML/pdfStore.nsf&docid=6AB8F698BB188543CA2583DA004245CC&agid=\(PrintDetailsPublic\)&actionid=1](https://www.ebs.tga.gov.au/servlet/xmlmillr6?dbid=ebs/PublicHTML/pdfStore.nsf&docid=6AB8F698BB188543CA2583DA004245CC&agid=(PrintDetailsPublic)&actionid=1) [Accessed 19th June 2019].
7. Pipino, G., Risitano, S. et al (2019). 'Microfractures and hydrogel scaffolds in the treatment of osteochondral knee defects: A clinical and histological evaluation'. *J Clin Orthop Trauma*, 10 (1), 67-75.
8. Oligo Medic (?). *JointRep - Injectable Implant*. [Internet]. Oligo Medic. Available from: <http://oligomedic.com/en/jointrep-2/> [Accessed 19th June 2019].
9. S.A., O. B. (?). *JointRep™ Medical Professional*. [Internet]. Ortho Biomedica S.A. Available from: <http://joint-repair.com/medical-professional/> [Accessed 17th June 2019].
10. U.S. National Library of Medicine (2019). *Knee microfracture surgery*. [Internet]. U.S. National Library of Medicine. Available from: <https://medlineplus.gov/ency/article/007255.htm> [Accessed 4th September 2019].
11. S.A., O. B. (?). *What is JointRep*. [Internet]. Ortho Biomedica. Available from: <http://joint-repair.com/what-is-jointrep/> [Accessed 2nd July 2019].
12. Jeuken, R. M., Roth, A. K. et al (2016). 'Polymers in Cartilage Defect Repair of the Knee: Current Status and Future Prospects'. *Polymers (Basel)*, 8 (6).
13. Steinwachs, M., Cavalcanti, N. et al (2019). 'Arthroscopic and open treatment of cartilage lesions with BST-CARGEL scaffold and microfracture: A cohort study of consecutive patients'. *Knee*, 26 (1), 174-84.
14. Piramal Life Sciences (?). *The sound science of cartilage regeneration. BST CARGEL*. [Internet]. Piramal Life Sciences. Available from: [http://www.ripollydeprado.com/uploaded/pdf/tecnicas/BST-CarGel%20Surgeon%20brochure%20and%20folder%20\(English%20version%20pdf\).pdf](http://www.ripollydeprado.com/uploaded/pdf/tecnicas/BST-CarGel%20Surgeon%20brochure%20and%20folder%20(English%20version%20pdf).pdf) [Accessed 19th June 2019].
15. Smith & Nephew (?). *CARGEL*. [Internet]. Smith & Nephew. Available from: <https://www.smith-nephew.com/key-products/sports-medicine/bst-cargel/> [Accessed 19th June 2019].
16. Stanish, W. D., McCormack, R. et al (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 (18), 1640-50.

17. Australian Government Department of Health (2015). *Public Summary for ARTG Entry 252732. Smith & Nephew Pty Ltd - BST CarGel - Cartilage biomatrix implant*. [Internet]. Australian Government Department of Health, Therapeutic Goods Administration

Available from:
[https://www.ebs.tga.gov.au/servlet/xmlmillr6?dbid=ebs/PublicHTML/pdfStore.nsf&docid=F0D60094F83D846CA257E9800422AEC&agid=\(PrintDetailsPublic\)&actionid=1](https://www.ebs.tga.gov.au/servlet/xmlmillr6?dbid=ebs/PublicHTML/pdfStore.nsf&docid=F0D60094F83D846CA257E9800422AEC&agid=(PrintDetailsPublic)&actionid=1) [Accessed 19th June 2019].
18. Geistlich Pharma AG (2019). *Chondro-Gide*. Available from: <https://www.geistlich-pharma.com/en/orthopaedic/products/chondro-gide/user-benefits/> [Accessed 3rd July 2019].
19. Geistlich Pharma AG (2019). *Chondro-Gide. AMIC in the knee. Autologous Matrix Induced Chondrogenesis*. [Internet]. Geistlich Pharma AG. Available from: https://www.geistlich-pharma.com/fileadmin/content/Geistlich_Pharma/Pdf/pdf_Orthopaedical/AMICKnee_en.pdf [Accessed 3rd July 2019].
20. Geistlich Pharma AG (2019). *The Chondro-Gide product range for different indications*. [Internet]. Geistlich Pharma AG. Available from: <https://www.geistlich-pharma.com/en/orthopaedic/products/chondro-gide/product-range/> [Accessed 3rd July 2019].
21. Australian Government Department of Health (2007). *Public Summary for ARTG Entry 146887, Geistlich Pharma Australia Pty Ltd - Chondro Gide - Orthopaedic cartilage repair membrane*. [Internet]. Australian Government Department of Health, Therapeutic Goods Administration. Available from:
[https://www.ebs.tga.gov.au/servlet/xmlmillr6?dbid=ebs/PublicHTML/pdfStore.nsf&docid=6B14B4D5F5E9DD94CA2577DD000299FF&agid=\(PrintDetailsPublic\)&actionid=1](https://www.ebs.tga.gov.au/servlet/xmlmillr6?dbid=ebs/PublicHTML/pdfStore.nsf&docid=6B14B4D5F5E9DD94CA2577DD000299FF&agid=(PrintDetailsPublic)&actionid=1) [Accessed 3rd July 2019].
22. International Cartilage Regeneration and Joint Preservation Society (?). *Mosaicplasty*. [Internet]. International Cartilage Regeneration and Joint Preservation Society. Available from: <https://cartilage.org/patient/about-cartilage/cartilage-repair/mosaicplasty/> [Accessed 4th September 2019].
23. Medical Services Advisory Committee (2010). *MSAC application 1140: Matrix-induced autologous chondrocyte implantation and autologous chondrocyte implantation*, Medical Services Advisory Committee, Australia
<http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1140-public>.
24. Mithoefer, K., Saris, D. B. F. et al (2011). 'Guidelines for the Design and Conduct of Clinical Studies in Knee Articular Cartilage Repair: International Cartilage Repair Society Recommendations Based on Current Scientific Evidence and Standards of Clinical Care'. *Cartilage*, 2 (2), 100-21.
25. Roos, E. M., Engelhart, L. et al (2011). 'ICRS Recommendation Document: Patient-Reported Outcome Instruments for Use in Patients with Articular Cartilage Defects'. *Cartilage*, 2 (2), 122-36.