

**NATIONAL INSTITUTE FOR HEALTH AND CARE  
EXCELLENCE**

**Appraisal consultation document**

**Autologous chondrocyte implantation for  
repairing symptomatic articular cartilage  
defects of the knee (including a review of  
TA89)**

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using autologous chondrocyte implantation within the applicable licensed indications for repairing symptomatic articular cartilage defects of the knee in the NHS in England. The Appraisal Committee has considered the evidence submitted and the views of non-company consultees and commentators, clinical experts and patient experts.

**This document has been prepared for consultation with the consultees.** It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the Committee. NICE invites comments from the consultees and commentators for this appraisal (see section 10) and the public. This document should be read along with the evidence base (the [Committee papers](#)).

The Appraisal Committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

**Note that this document is not NICE's final guidance on these technologies. The recommendations in section 1 may change after consultation.**

After consultation:

- The Appraisal Committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the Committee will also consider comments made by people who are not consultees.
- After considering these comments, the Committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using autologous chondrocyte implantation in the NHS in England.

For further details, see the Guides to the technology appraisal process.

**The key dates for this appraisal are:**

Closing date for comments: 1 April 2015

Second Appraisal Committee meeting: 14 April 2015

Details of membership of the Appraisal Committee are given in section 9, and a list of the sources of evidence used in the preparation of this document is given in section 10.

**Note that this document is not NICE's final guidance on these technologies. The recommendations in section 1 may change after consultation.**

## **1 Appraisal Committee's preliminary recommendations**

- 1.1 Autologous chondrocyte implantation is recommended only in research for repairing symptomatic articular cartilage defects of the knee. Research should include clinical trials and observational studies designed to measure the long-term benefits of autologous chondrocyte implantation.

## **2 Clinical need and practice**

- 2.1 The ends of the femur, tibia and the underside of the patella (kneecap) are covered with articular cartilage, a type of hyaline cartilage. Hyaline cartilage is normally very smooth, promoting frictionless movements of the joints and also acting as a shock absorber. The cells within hyaline cartilage are called chondrocytes. These are responsible for producing and maintaining the cartilage matrix, formed mainly from collagen. Cartilage has no blood and nerve supply, so has a limited potential to repair itself.
- 2.2 Cartilage damage can be caused by injury or arthritis, or it can occur spontaneously. Cartilage damage may also arise because of knee instability or abnormal unbalanced pressures, for example after an injury to a ligament or meniscal cartilage. Obesity may also cause knee cartilage damage. In young people the most common cause of hyaline cartilage damage is sporting injuries. Symptoms associated with the loss of hyaline cartilage include pain, swelling, instability and joint locking. In addition, damage to

the cartilage and surrounding tissues can cause osteoarthritis and lead to a need for partial or total knee replacement surgery in later life. People who have a knee replacement have an increased mortality risk during the surgery. Cartilage damage can be described by size (area) and graded by depth. Commonly used scoring systems include the international cartilage repair society (ICRS) grading system, and the Outerbridge system.

- 2.3 It is estimated that around 10,000 people need treatment for cartilage damage every year in the UK. Between 200 and 500 of these have cartilage defects suitable for autologous chondrocyte implantation.
- 2.4 Cartilage injuries can significantly impact quality of life. In professional athletes, and in people who have physically demanding jobs, cartilage injuries may lead to loss of employment. Current treatment options aim to relieve symptoms. Treatments include knee lavage with or without debridement (removal of damaged cartilage), re-establishing the articular surface (microfracture, mosaicplasty and autologous chondrocyte implantation [ACI]), osteotomy, and knee replacement. Microfracture involves drilling small holes through the bone under the damaged cartilage to allow bone marrow cells to fill the damaged area and to differentiate into chondrocytes. However, fibrocartilage formed in this way is considered to be less durable than natural hyaline cartilage. Microfracture is normally used for lesion sizes of less than 13 cm<sup>2</sup>. Mosaicplasty (also known as osteochondral transplantation) involves transplanting small sections of cartilage and underlying bone from a less weight-bearing part of the knee into the damaged area. Mosaicplasty is used for small areas of damage (less than 4 cm<sup>2</sup>). In ACI, chondrocytes are harvested from the knee, cultured, and implanted into the area of the damaged cartilage (see section 2.5). Osteotomy and knee

replacement are reserved for larger lesions and those where cartilage repair has failed can be treated by osteotomy (realigning of the knee) and knee replacement.

2.5 ACI involves taking a biopsy of cartilage from a less weight-bearing part of the affected knee during arthroscopic surgery. Chondrocytes from the cartilage are then cultured in a laboratory to increase their number. Chondrocytes can be cultured traditionally ('traditional ACI') or by using biomarkers to select cells most likely to produce hyaline cartilage; these cells are called characterised chondrocytes. Finally, the chondrocytes are implanted into the area of damaged cartilage during a second surgical procedure, in the hope that they will repair the damaged area. ACI is not used for unstable or arthritic joints.

2.6 ACI has evolved over many years. In the first generation of ACI, the implanted cultured chondrocytes were covered with a cap made from periosteum (ACI-P), fibrous tissue that covers bones. In the second generation the cap was made from collagen (ACI-C). The third generation of ACI involved seeding the chondrocytes onto a porcine collagen membrane (ACI-M) to avoid chondrocytes leaking around the cap. The branded MACI product is a third generation ACI – provided in the form of a membrane that has been seeded with chondrocytes). The branded product ChondroCelect is provided in a vial, and can be used with a collagen cap, a periosteal cap or on a membrane. ChondroCelect and traditional ACI require a separate commercially available membrane in order to be used as a third generation ACI.

2.7 There are no UK guidelines or internationally accepted treatment guidelines on how and when to treat cartilage lesions. A survey published by Steinwachs et al. (2011), involving 242 European orthopaedic surgeons, recommends debridement with or without microfracture as a first choice treatment for full-thickness cartilage

lesions of up to 3 cm<sup>2</sup>. For treating lesions larger than 3 cm<sup>2</sup>, ACI (any generation) was preferred by 33.5% of the experts, microfracture by 19% and debridement by 15%. Current NICE technology appraisal guidance on [the use of autologous chondrocyte implantation for the treatment of cartilage defects in the knee joints](#) does not recommend ACI for treating articular cartilage defects of the knee except in the context of ongoing or new clinical studies. This is because, at the time of the appraisal in 2005, the data available were too limited to draw conclusions about the cost effectiveness of ACI compared with treatment alternatives.

### 3 The technologies

#### ChondroCelect

- 3.1 The ChondroCelect product used in autologous chondrocyte implantation (ACI) contains characterised viable autologous human chondrocytes at a concentration of 10,000 cells per microlitre and is provided in a vial. ChondroCelect received regulatory approval in October 2009 and has a UK marketing authorisation for the repair of single symptomatic cartilage defects of the femoral condyle of the knee (International Cartilage Repair Society grade III or IV) in adults. The [summary of product characteristics](#) states that ‘demonstration of efficacy is based on a randomised controlled trial evaluating the efficacy of ChondroCelect in patients with lesions between 1-5 cm<sup>2</sup>. The summary of product characteristics does not specify one particular cap or matrix, but notes that the clinical data that support the marketing authorisation are based on using ChondroCelect with a periosteal cap. It also notes that, although the safety of ChondroCelect has not been evaluated with a collagen cap or seeded onto a membrane, it may also be used with them.

- 3.2 The summary of product characteristics lists the following as the most frequently occurring adverse reactions related to ChondroCelect: arthralgia (joint pain), cartilage hypertrophy (overgrowth of cartilage), joint crepitation (popping and cracking sounds in the joint), joint effusion (extra fluid in the joint), treatment failure and delamination (separation of the uncalcified articular cartilage from the calcified cartilage). The summary of product characteristics also lists the following adverse reactions related to surgical intervention of the knee: postoperative joint swelling, arthralgia, pyrexia, arthrofibrosis (excessive scar tissue) and decreased range of motion of the knee. For full details of adverse reactions and contraindications, see the [summary of product characteristics](#).
- 3.3 The list price of the ChondroCelect product is £18,301 for a vial containing 4 million cells in 0.4 ml implantation suspension (price excluding VAT; eMC Dictionary of Medicines and Devices Browser). Costs may vary in different settings because of negotiated procurement discounts.

## **MACI**

- 3.4 MACI (matrix associated chondrocyte implantation) uses characterised viable autologous chondrocytes seeded onto a porcine-derived type I/III collagen membrane. The implant has a density of 500,000 to 1,000,000 cells per cm<sup>2</sup>, which the surgeon trims to the size and shape of the person's cartilage lesion. MACI received regulatory approval in Europe in June 2013 and has a marketing authorisation for 'the repair of symptomatic, full-thickness cartilage defects of the knee (grade III and IV of the modified Outerbridge Scale) of 3 to 20 cm<sup>2</sup> in skeletally mature adult patients'. MACI is, by definition, a third generation ACI technique.

- 3.5 The summary of product characteristics lists the following as the most frequently occurring adverse reactions associated with MACI: symptomatic graft hypertrophy and graft delamination (complete or partial). The summary of product characteristics also lists the following adverse reactions related to surgical intervention of the knee: haemarthrosis (bleeding into joint spaces), arthrofibrosis, localised surgical site inflammation, localised surgical site infection and thromboembolic events. For full details of adverse reactions and contraindications, see the [summary of product characteristics](#).
- 3.6 The list price quoted in the submission for the MACI product is £16,226 per implant (price excluding VAT). Costs may vary in different settings because of negotiated procurement discounts.

### **Traditional ACI**

- 3.7 Traditional ACI does not select (characterise) cells for culture that are most likely to make hyaline cartilage. The OsCell John Charnley Laboratory is an NHS laboratory at the Robert Jones and Agnes Hunt (RJAH) Orthopaedic Hospital in Oswestry, England. The facility has cultured and provided autologous chondrocytes for use in ACI since 1997, and is the only NHS facility to do so. The facility has a Hospital Exemption Licence that enables OsCell to supply chondrocytes for use in ACI in a hospital under the professional responsibility of a medical practitioner. The OsCell submission notes that the technology is indicated for use in 'patients with a significantly symptomatic chondral or osteochondral defect in the knee where any underlying mal-alignment, instability or loss of meniscus is also corrected'. The cells are supplied as prescribed by the surgeon, from 1 to 20 million cells in a sterile syringe in 0.2 to 0.6 ml of the patient's own serum. OsCell's submission noted that 30 to 40 people have ACI each year at RJAH. OsCell stated that it prefers to implant cultured chondrocytes under a sutured collagen cap (second generation

ACI-C) or seed cells onto a membrane (third generation ACI-M) for procedures in which suturing is difficult. The OsCell submission states that producing cells costs £4125 per patient.

## 4 Evidence and interpretation

The Appraisal Committee (section 10) considered evidence from a number of sources (section 11).

### *Clinical effectiveness*

#### **Assessment Group's systematic reviews of clinical evidence**

4.1 The Assessment Group carried out a systematic review for clinical effectiveness, searching specifically for existing reviews that focused on comparing the effectiveness of autologous chondrocyte implantation (ACI; any generation) with microfracture. The Assessment Group identified 12 relevant systematic reviews, which included primary studies of:

- first generation ACI-P compared with second generation ACI-C
- first or second generation ACI compared with MACI (third generation)
- open compared with arthroscopic ACI
- first or second generation ACI compared with mosaicplasty
- ACI (any generation) compared with microfracture.

The Assessment Group commented that the studies within the reviews were heterogeneous: follow-up was between 6.5 months and 7.5 years; mean age of the patients was between 26.4 and 40.4 years and between 47% and 80% of them were men; mean lesion size was between 1.9 and 6.4 cm<sup>2</sup>; and duration of symptoms before the intervention was between 1.5 and 10 years. The Assessment Group also commented that the reviews had various limitations including: poor quality (because of small sample

sizes, inadequate durations of follow-up, lack of allocation concealment, not enough information on method of randomisation, losses to follow-up and blinding of assessment scoring); differences in patient characteristics between studies; variations in previous surgery, and the outcomes measured. Therefore the Assessment Group considered the results of the reviews to be inconclusive on the effectiveness of ACI compared with microfracture.

4.2 The Assessment Group summarised its findings of the systematic review as follows:

- ACI may take longer than other interventions to reach maximal knee function.
- Symptomatic relief provided by ACI may last longer than microfracture.
- First generation ACI-P, compared with second generation ACI-C, was associated with a higher rate of graft hypertrophy and higher failure rates.
- Outcomes were better for younger people, those who were more active, those with shorter duration of symptoms and those who had not had previous knee surgery for their condition.
- People with small lesions had better outcomes than people with bigger lesions.
- Among people with larger lesions, ACI appeared to produce better outcomes compared with microfracture.

### **Clinical effectiveness evidence from company submissions**

4.3 NICE received submissions for ChondroCelect (SOBi), MACI (Aastrom), and OsCell (Robert Jones and Agnes Hunt [RJAH] Orthopaedic Hospital).

### ***ChondroCelect***

- 4.4 The submission supporting ChondroCelect provided evidence of clinical effectiveness from 4 sources: a randomised controlled trial, TIG/ACT/01/2000; a 'compassionate use' case series; a registry-based cohort study, TGX001-2011; and data from a Belgian reimbursement scheme.
- 4.5 The TIG/ACT trial was an unblinded randomised controlled trial comparing first generation (ACI-P) ChondroCelect (n=57) with microfracture (n=61) in adults between 18 and 50 years with a single symptomatic cartilage defect of between 1 and 5 cm<sup>2</sup> of the femoral condyles. The primary outcome of the trial was the change from before the ACI procedure, measured by the overall Knee injury and Osteoarthritis Outcome Score (KOOS) with scores transformed to a scale of 0 to 100, with 0 representing extreme knee problems and 100 representing no knee problems. The KOOS score comprises 5 subdomains: 1) activities of daily living; 2) pain; 3) symptoms/stiffness; 4) knee-related quality of life and function; 5) sports and recreational activities. The trial also collected health-related quality of life using the SF-36 questionnaire. Previous knee procedures had been carried out in 37% of those in the ACI group and 21% of those in the microfracture group. At up to 60-month follow-up, ChondroCelect was associated with a greater overall KOOS score of 21.17 compared with 14.07 for microfracture, which was not statistically significant (p=0.068). ACI was associated with a trend towards greater KOOS score compared with microfracture for each subdomain. SF-36 values were better for ChondroCelect than for microfracture, but there was no significant difference between treatment groups. Radiographic results from 49 patients taken at baseline and at 60 months showed no statistically significant difference between the 2 groups. Treatment failure, defined as a re-intervention that was necessary because of the persistence or

recurrence of symptoms, occurred in 13.7% of people in the ChondroCelect group and 16.4% of people in the microfracture group (difference not statistically significant). Over 5 years, more people in the ACI group experienced at least 1 related adverse event compared with the microfracture group (82% compared with 62%). In a predefined subgroup analysis of people with onset of symptoms within 3 years, patients randomised to ChondroCelect improved significantly more than people randomised to microfracture (difference in KOOS score 10.69 [95% confidence interval [CI] 1.30 to 20.07, p=0.026]).

- 4.6 The Assessment Group commented that TIG/ACT was a good-quality trial. However, the Assessment Group regards ACI-P (used in TIG/ACT) as obsolete because it has no obvious clinical advantages over second or third generation ACI, needs more time in surgery, and is associated with higher subsequent costs (for example, shaving of hypertrophy).
- 4.7 The 'compassionate use' case series was a study without a comparison (control) group of 370 people with symptomatic articular cartilage defects of the knee, all of whom were treated by second generation (ACI-C) ChondroCelect. There were no predefined entry criteria. The outcomes were the Clinical Global Impression measures of improvement (CGI-I) and efficacy (CGI-E). The CGI-I results, ranging from very much worse to very much improved, showed good outcomes (much improved or very much improved) in 68% of people. The CGI-E outcomes ranged from unchanged or worse to very good, and indicated that 38% of people had very good results, 36% had moderate improvement, 12% had slight improvement and 11% were unchanged or worse.
- 4.8 The ongoing registry-based cohort study TGX001-2011 is collecting data in Belgium and the Netherlands where ACI using ChondroCelect is publically funded. From the cohort of 308 people,

153 reached 6 months or more of follow-up. Interim analysis showed an increase in KOOS score at up to 36 months, but the company that manufactures ChondroCelect did not provide the number of patients at each follow-up period. Six treatment failures (defined as the need for a re-intervention for more than 20% of the treated area) and 2 deep vein thromboses were among a total of 17 serious adverse events observed.

- 4.9 Another source of evidence provided by the company manufacturing ChondroCelect includes observational data from the Belgian reimbursement scheme of ChondroCelect procedures carried out in Belgium over a 3-year period from May 2011 to April 2014, and a record of the number of treatment failures during this time. The data showed 51 procedures were done in year 1, 93 procedures in year 2 and 110 procedures in year 3. Treatment failure occurred in 2 patients within 12 months of the procedure and in a further 2 patients between 12 and 24 months. The company reported that of the 51 procedures done in year 1, there had been no treatment failures at 3-years follow-up.

### **MACI**

- 4.10 The submission supporting MACI described clinical evidence primarily from 3 sources: a randomised controlled trial, SUMMIT (including the SUMMIT extension study); a randomised controlled trial, Basad et al. (2010); and an indirect comparison of MACI with first generation ACI-P.
- 4.11 SUMMIT was an open-label (unblinded), multicentre (16 European sites) randomised controlled trial comparing MACI with microfracture in 144 adults aged 18 to 55 years with symptomatic defects of knee cartilage. Patients had a mean age of 33.8 years and a mean lesion size of 4.8 cm<sup>2</sup> (inclusion criterion for lesion size was 3 cm<sup>2</sup> or more). Previous knee surgery was performed in 90%

of people in the MACI group and 84% of people in the microfracture group. The co-primary efficacy end point was the change in the KOOS pain and function sub-scores from baseline measured at 2- year follow-up (n=137). There was significantly greater improvement from baseline to 2 years in mean KOOS pain and function sub-scores with MACI compared with microfracture (pain: difference between ACI and microfracture 11.76,  $p=0.001$ ; function: difference between ACI and microfracture 11.41,  $p=0.001$ ). There was a similar improvement in the pain and function scores in a post-hoc subgroup analysis of people with a lesion size of less than 4 cm<sup>2</sup>. A greater improvement in secondary outcomes was also observed for patients randomised to MACI compared with microfracture on the KOOS subscales of activities of daily living (difference between ACI and microfracture 12.01,  $p<0.001$ ), knee-related quality of life (difference between ACI and microfracture 8.98,  $p=0.029$ ), and other symptoms (for example, swelling, restricted range of motion [7 items]; difference between ACI and microfracture 11.61,  $p=0.001$ ). The SUMMIT study was followed by an ongoing 3-year extension study: the details and interim results from the first year of follow-up were presented by the company and marked as academic in confidence.

4.12 The Assessment Group commented that the efficacy of ACI may be more effective compared with microfracture than observed in the SUMMIT study for 2 reasons. Patients in the MACI group, compared with those in the microfracture group, had:

- symptoms for a longer length of time
- more previous knee surgeries (not including diagnostic arthroscopy), which have been shown to reduce the efficacy of subsequent ACI procedures.

- 4.13 Basad et al. was a randomised controlled trial comparing MACI (n=40) with microfracture (n=20) in adults aged 18 to 50 years. Arthroscopy was done in all patients to assess eligibility for the study, which included a single symptomatic chondral lesion of the femur or patella of between 4 and 10 cm<sup>2</sup>. Previous surgery, if any, was not reported. People in the MACI group had symptoms for 2.2 years and those in the microfracture group for 2.5 years. The primary outcome measures included the Tegner, Lysholm and International Cartilage Repair Society (ICRS) scale scores. The authors did not define failure. All patients had rehabilitation after surgery. Fifty-six people (39 in the MACI group and 17 in microfracture group) completed at least 6 months of follow-up and 48 people (33 in the MACI group and 15 in the microfracture group) completed 2 years of follow-up. The Basad et al. trial showed a significant difference between baseline and 24-month post-operative scores for both MACI and microfracture for the Lysholm, Tegner, surgeon ICRS scores and patient ICRS questionnaire (p<0.0001). MACI was associated with a significantly greater improvement from baseline compared with microfracture in Lysholm (p=0.005), Tegner (p=0.04), ICRS patient (p=0.03) and ICRS surgeon (p=0.02) at 24-month follow-up.
- 4.14 The Assessment Group rated the quality of the Basad et al. (2010) trial as poor using the modified Coleman methodology score, although it stated that this was partly because the authors failed to report items. The Assessment Group commented that the authors had significant experience with ACI so their results may be better than those recorded elsewhere. The Assessment Group also commented that the patients in the Basad et al. trial had a fairly short duration of symptoms, which may improve outcomes after ACI and would affect the generalisability of the study.

***Traditional ACI***

4.15 The OsCell submission reported clinical effectiveness evidence for traditional ACI from 2 sources: a randomised controlled trial ACTIVE and a cohort study, REACT. The ACTIVE trial is an ongoing, multicentre, open-label randomised controlled trial of ACI (n=195; including first, second and third generation ACI) compared with standard treatment (n=195). Standard treatment can include microfracture, microfracture plus collagen membrane, mosaicplasty, debridement, abrasion, drilling, or bone graft in people with (a) symptomatic chondral defect(s) on the medial or lateral femoral condyle or trochlea/patella whose condition has failed previous treatment and were considered suitable for ACI. Methodological details given on the trial, including the analytical approach and reporting of relevant numbers of outcomes, were limited. Furthermore, the investigators designated the study details for the ACTIVE trial as academic-in-confidence. The Assessment Group rated the quality of the ACTIVE study as good using the modified Coleman methodology score. OsCell's submission included interim clinical data from the ACTIVE trial after 5-year follow-up. Using the outcome of independently assessed Lysholm scores there was no statistically significant difference between the 2 treatment groups during the first 4 years. However, at year 5, the mean Lysholm score of people treated by ACI (73.1) was higher than that of people in the control group (66.6;  $p=0.03$ ). Using the outcome of patient-assessed Lysholm scores there was no statistically significant difference between the 2 treatment groups during the first 5 years. Further interim results for the ACTIVE trial were designated academic-in-confidence.

OsCell provided details of the REACT study, a cohort study with up to 15 years of follow-up of 366 patients with chondral or osteochondral defects treated by traditional ACI (not limited to the knee – hips and ankles were also treated) in the RJAH Orthopaedic

Hospital, Oswestry. OsCell marked these results as academic in confidence.

### **Indirect comparison**

4.16 The company that manufactures MACI submitted an indirect comparison of MACI with first generation ACI techniques. Using microfracture as the common comparator, the indirect comparison included the 2-year data from SUMMIT for (third generation) MACI, and the TIG/ACT trial for first generation (ACI-P) with ChondroCelect. The indirect comparison showed no difference between first generation ACI-P and MACI in the likelihood of a response to treatment. The company that manufactures MACI also carried out an indirect comparison to compare MACI with mosaicplasty. This analysis used results from the Stanmore trial, published by Bentley et al. (2003), a randomised controlled trial comparing ACI (n=58) with mosaicplasty (n=42). Functional assessment using the modified Cincinnati Knee and Stanmore functional rating scores and objective clinical assessment showed 'good' or 'excellent' results in 88% after first generation (ACI-P) or second generation (ACI-C) ACI compared with 69% after mosaicplasty. In a post-hoc analysis the company classified people with 'good' or 'excellent' results as responders, and showed that people who were randomised to mosaicplasty had a significantly lower likelihood of having a response compared with people who were randomised to second generation ACI (relative risk 0.79, CI 0.63 to 0.98). Based on the finding that there was no difference in treatment response rate between first generation ACI-P and MACI, the company argued that MACI would also be superior to mosaicplasty.

### **General comments on the clinical effectiveness evidence made by the Assessment Group**

- 4.17 The Assessment Group noted evidence from a study by Minas and colleagues (2009) that prior microfracture makes subsequent ACI less effective. The Assessment Group noted that this evidence implies that the benefits of ACI as a first procedure may be greater than the benefits observed in studies in which ACI followed previous knee surgery.
- 4.18 The Assessment Group commented on the strengths and weaknesses of the clinical data, stating that, compared with previous appraisals, more longer-term data and data from several new trials are now available. The ACTIVE trial has data from up to 8 years follow-up (and will have 10 years of follow-up on all patients when completed), the TIG/ACT trial has 5 years of follow-up, and the 2 trials of MACI compared with microfracture currently have 2 years of follow-up. The Assessment Group stated that the evidence is limited by the evolving nature of the technology, and because the longest-term data come from early versions of ACI that have largely been superseded. The Assessment Group stated that most, but not all, studies suggest that ACI is more effective than microfracture if it is used soon after the cartilage injury.

### ***Cost effectiveness***

- 4.19 The Assessment Group identified 6 studies that included full economic analyses (including economic models) on the use of ACI, microfracture and mosaicplasty for repairing symptomatic articular cartilage defects of the knee. It commented that each study lacked long-term clinical follow-up data and good quality-of-life data.

### **ChondroCelect submission – cost effectiveness**

- 4.20 The ChondroCelect submission presented a de novo Markov economic model. The model cycle length was 1 month, average

age was 33 years and the model time horizon reflecting a lifetime was 75 years. The model structure allowed successes of ACI to be temporary or permanent. If either microfracture or ACI failed, the patient had debridement. Thereafter, the patient then either had a second repair (microfracture only), or was offered pain relief. If the second repair failed the patient had debridement and pain relief. The company modelled effectiveness using data from the TIG/ACT trial on the time-to-treatment failure. Utility scores were taken from the TIG/ACT trial and also from a paper by Gerlier et al. (2010) in which the authors analysed KOOS scores and responses to the SF-36 questionnaire collected up to 60 months post-surgery.

- 4.21 The model used NHS reference costs and a cost for ChondroCelect of £16,000. The cost of procedures included the costs of surgery, inpatient stays and physiotherapy follow-up. The cost of the first procedure – cell harvest – was £722.45, and the cost of the second procedure – cell implantation – was £109.65 (this was assumed to be conducted in an outpatient setting). The costs of adverse events were not included in the model as there were no key differences between treatment arms in the TIG/ACT trial. The company chose microfracture as the only comparator in the model. The key assumptions of the model were that, compared with microfracture, fewer patients who had ACI needed second repairs and had a longer duration of success (which in turn postponed the knee replacements). The total cost of ACI was £22,586, and the total cost of microfracture was £13,547. ACI was associated with an additional 1.29 QALYs compared with microfracture, and the corresponding ICER was £7077 per QALY gained. In sensitivity analyses, the main driver of cost effectiveness was the time to failure of the first repair. When the company reduced the time horizon to 5 years the ICER increased to £291,867 per QALY gained. In addition, the company carried out a sensitivity analysis in which half of the people having either first

repair would have a microfracture as second repair, which increased the ICER from the base case of approximately £7000 to £24,490 per QALY gained.

***Assessment Group comments***

4.22 The Assessment Group stated that the economic model in the ChondroCelect submission was logical, and was backed by mostly plausible assumptions. It stated that the company had underestimated the cost of implanting cells because surgeons would perform the procedure as a day case and not an outpatient visit. It commented that the utility values were plausible and that it was reasonable to assume that microfracture is the only relevant comparator for ACI.

**MACI submission – cost effectiveness**

4.23 The company manufacturing MACI did not present a cost-effectiveness analysis, but provided a budget impact and costing forecast for England and Wales based on the assumption of 500 ACI procedures per year, half of which would be with MACI. It explored 2 scenarios: 1 with MACI or ACI as the first procedure, the other with microfracture as the first procedure, and calculated the difference in costs between the 2 scenarios. Based on data for failure rates of each procedure from the SUMMIT trial, the company estimated that using MACI or ACI would save the NHS in England from £5.9 million in year 1 to £8.3 million in year 5. These savings were largely because patients who have MACI or ACI need fewer operations over time than patients who have microfracture.

***Assessment Group comments***

4.24 The Assessment Group commented that the budget impact cost calculations provided in the MACI submission seemed plausible.

### **OsCell submission – cost effectiveness**

4.25 OsCell submitted an analysis of costs and benefits based on the ACTIVE trial but did not present an economic model. It stated costs for ACI according to the National Tariff Payment System (2014–15) as reimbursed to the RJAH Orthopaedic Hospital. This included the cost of operations, hospital stays, cells and any further implants. It assumed a cost for the first ACI procedure of cell harvesting of £2398 and a cost for the second stage procedure of cell implantation of £6876 (which included the cost for cells based on production by OsCell of £4125). The total cost of ACI was therefore £9274, or £9565 when taking into account an additional ‘market forces factor’ (a nationally determined variation to the national price). OsCell estimated that the incremental cost of ACI over microfracture was £7094. The OsCell submission presented a preliminary analysis of quality of life (EQ-5D) data from 8-year follow-up of the ACTIVE trial. These data showed little difference in QALYs between ACI and microfracture for the first 4 years; thereafter, EQ-5D results were better for the ACI group compared with the microfracture group leading to a large incremental QALY gain at 8 years based on 29 people in the ACI group and 27 people in the control group. OsCell commented that it was not possible to draw robust conclusions from 27 and 29 people respectively, but suggested the results were indicative and consistent across the 2 arms of the trial. OsCell estimated the ICER for ACI compared with microfracture at around £6000 per QALY gained.

### ***Assessment Group comments***

4.26 The Assessment Group commented that it was not clear how OsCell converted the reported EQ-5D results to QALYs. The Assessment Group also noted that the utility values reported from the ACTIVE trial were markedly lower than those reported from the TIG/ACT trial using ChondroCelect.

### Assessment Group report – cost effectiveness

- 4.27 The Assessment Group constructed a Markov model to estimate the cost effectiveness of ACI as a class compared with microfracture. The Assessment Group assumed that all ACI interventions (that is, ChondroCelect, MACI and OsCell) were equally effective. The model used a lifetime horizon of 100 years, a cycle length of 1 year and transitions between each health state at the end of each cycle. The model included a hypothetical cohort of 1000 people with symptomatic articular cartilage defects of the knee, with a starting average age of 33 years who have a first repair with either an ACI or microfracture. The analysis was conducted from the perspective of the NHS and personal social services. An annual discount rate of 3.5% was applied to both costs and outcomes. The main comparison was between ACI and microfracture.
- 4.28 The Assessment Group's model included the following health states: 'primary repair', 'successful primary repair', 'second repair', 'successful second repair', and 'no further repair'. The model also included health states for 'first knee replacement', 'successful first knee replacement', and 'no further knee replacement'. It also had health states for 'further knee replacement' and 'successful further knee replacement'. The Assessment Group's model allowed for a number of outcomes after the first or second repair, including permanent success, temporary success or failure. The Assessment Group defined permanent success as staying in the successful first or second repair health states until death. The Assessment Group defined temporary success as having no symptoms for a number of years, but after a while the repair fails and the patient moves to the failure of primary repair health state. The Assessment Group defined failure as a patient requiring another repair, or deciding against another repair (and treating symptoms with pain medication). The Assessment

Group acknowledged that people in whom a first or second repair failed would probably develop osteoarthritis, and may have 1 or more knee replacements later in life. It assumed that people over 55 years would not have an ACI. The Assessment Group did not include adverse events as it considered that there were no important differences between ACI and microfracture.

4.29 For its base-case analysis, the Assessment Group chose data from the TIG/ACT trial of ChondroCelect and the SUMMIT trial of MACI, both of which compared ACI with microfracture. The Assessment Group used 3-year data from the TIG/ACT to estimate the rates of people moving from the primary (or second) repair health states to 1 of 4 states: the successful primary repair state, the second repair state, the successful secondary repair state or the no further repair state. The Assessment Group used 2-year progression rates from SUMMIT to estimate the rates of people who remained in the successful primary (or second) repair, or who moved from these states to the state of no further repair or the second repair health state. Using response rates from the SUMMIT study, the Assessment Group assumed that 87.5% of patients who had ACI as a primary procedure and 68.1% of patients who had microfracture as primary procedure did not need a second repair. The Assessment Group used data for knee replacement from the published literature, including the timing of knee replacement after the repair health states (from Knutsen et al, 2007), the transition probabilities for success and failure for people who needed knee replacements (from Gerlier et al. 2010 and Dong and Buxton 2006), and the increased mortality risk during surgery (from Mahomed et al. 2005).

4.30 Similar to the ChondroCelect model, the Assessment Group's model used utility values for knee repairs from the study by Gerlier et al. (2010); this study compared ACI with microfracture using

5-year data from the TIG/ACT trial that used the SF-36 questionnaire. The Assessment Group used 2 other studies to supplement utility values for knee replacement and knee arthroscopy. The mean utility value for people before a primary repair (ACI or microfracture) was 0.654. The mean utility value for people following a successful primary repair was 0.760 for the first year. For a person who had ACI a primary repair, the mean utility value (in the successful primary repair health state) was 0.817 from the second year after repair and onward. For people who had microfracture as a primary repair, the utility value was 0.817 from the second year until the fourth year after repair, after which the Assessment Group assumed that the utility would fall to the pre-surgical level of 0.654.

- 4.31 The Assessment Group estimated costs for the different procedures (ACI, microfracture, partial or total knee replacement) and for outpatient visits and rehabilitation as shown in table 1. The Assessment Group chose 2013 NHS reference costs supplemented, where possible, by a previous Health Technology Appraisal report on cartilage defects in knee joints (Clar et al, 2005). All unit costs were presented in pounds sterling (£) in 2012–13 prices.

**Table 1 Base-case mean costs used in the economic model**

Procedure	Information	Unit cost (£)	Source
ChondroCelect and MACI	Product including courier services and development of cell culture	16,000	Price for ChondroCelect stated in submission
	Procedure 1 – arthroscopy and cell harvest	710*	Clar et al. (2005)
	Procedure 2 – arthrotomy (day case)	1,030*	Clar et al. (2005)
	<i>Total cost</i>	17,740	
Microfracture	Procedure (inpatient)	3,020*	Clar et al (2005)
First TKR (PKR or TKR)	HRG code: HB21C – major knee procedures for non-trauma, category 2, without complications	5,676	NHS reference costs (2013)
Further TKR	Second TKR	12,959*	Clar et al. (2005)
Outpatient visit	HRG code: WF01A – non-admitted face-to-face consultant-led outpatient attendance	102	NHS reference costs (2013)
Rehabilitation	HRG code: REHABL2 – rehabilitation for joint replacement	256	NHS reference costs (2013)
Abbreviations: HRG, Healthcare Resource Group; PKR, partial knee replacement; TKR, total knee replacement			

\* Cost adjusted for inflation to 2012–13 prices

4.32 The Assessment Group used the approximate costs of ChondroCelect and MACI for the cost of ACI which included the costs associated with cell development, the ACI kit, staff time and transporting the cells to and from the laboratory. It assumed that both procedures (removing the cells and implanting them) could be performed as a day case. Conversely, the Assessment Group considered that the microfracture procedure would require an inpatient stay for pain control. Based on consultation with clinical experts, the Assessment Group included in its model the costs of rehabilitation and other outpatient visits in the first year (see table 2).

**Table 2 Base-case resource use for the Assessment Group’s economic model**

Components of model (over a year)	Procedure		
	Autologous chondrocyte implantation	Microfracture	Total knee replacement
Inpatient days	0	1	4.5
Outpatient visits	6	3	2
Rehabilitation visits	3	3	0

4.33 The Assessment Group used the term ACI as a generic term to cover all forms of ACI, assuming that they were equally effective. The base-case discounted ICERs are presented in table 3. For ACI compared with microfracture, the ICER ranged from £14,395 per QALY gained (if all people who needed a second repair had ACI) to £15,598 per QALY gained (all people who needed a second repair had microfracture).

**Table 3 Base-case resource use for the Assessment Group’s economic model**

Procedure	Incremental costs	Incremental QALYs	ICER (per QALY gained)
<b>Second repair with ACI:</b>			
Microfracture (ACI)*	-	-	-
ACI (ACI)*	£14,314	0.994	14,395
<b>Second repair with microfracture</b>			
Microfracture (Microfracture)*	-	-	-
ACI (Microfracture)*	£14,877	0.954	15,598

\*Procedure in parentheses denotes the choice of second repair ICER, incremental cost effectiveness ratio; QALY, quality adjusted life years

4.34 The Assessment Group carried out sensitivity analyses where it reduced the cell costs by 25%, 50% and 75%. In these analyses the ICERs for ACI compared with microfracture were reduced to about £11,000 (25% cost reduction), £7000 (50% cost reduction),

and £3000 per QALY gained (75% cost reduction). The Assessment Group carried out sensitivity analyses using utility data from the ACTIVE trial (as presented in the OsCell submission). If a patient needed a second repair and if this second repair was ACI, microfracture (as a first repair) dominated ACI; that is, ACI was less effective and more costly than microfracture. The Assessment Group stated that microfracture dominated ACI because the utility value for the fourth year after the procedure was higher for microfracture than for ACI. However, if a patient needed a second repair and if this second repair was microfracture, then ACI (as a first repair) has a lower ICER than microfracture (as a first repair) with an ICER in favour of ACI of nearly £26,000 per QALY gained. Other sensitivity analyses carried out by the Assessment Group included changing the time horizon, using a day-case rate for microfracture and improving the success rate of microfracture. The results of these analyses showed that the model was robust to most parameters tested, although it was sensitive to the time horizon. A shorter time horizon of 10 years resulted in the ICER for ACI compared with microfracture rising to around £26,000 per QALY gained (if any second repairs were ACI), and to around £27,000 per QALY gained (if any second repairs were microfracture). This effect was a result of the costs of the ACI procedure occurring at the start and the benefits of ACI not being realised until later; using time horizons of 50, 40, 30 and 20 years all resulted in ICERs well below £20,000 per QALY gained. When the Assessment Group used an average starting age of 45 years rather than 33 years, the ICER for ACI decreased if it were used as a first repair.

- 4.35 The Assessment Group carried out additional analyses in an addendum to the assessment report. When logical inconsistencies within some of the transition probabilities were removed from the model (so that a second repair with ACI after microfracture was as

effective as second repair with ACI after ACI, and a second repair with microfracture after ACI was as effective as a second repair with microfracture after microfracture) the ICERs were very similar to those of the base case. When the utility value at year 5 and beyond for the microfracture success state was set to 0.817 the ICER increased from around £15,000 to over £20,000 per QALY gained. A sensitivity analysis where the utility of the 'no further repair' health state was a mid-point between failure and success (0.74), increased the ICER from around £15,000 to around £20,000 per QALY gained.

- 4.36 Based on its sensitivity analyses, the Assessment Group stated that the key drivers in the base case were the cost of cells for ACI and how long patients benefitted from ACI or microfracture. In general, following the first few years after treatment, ACI provided a greater gain in QALYs and fewer costs to the NHS because fewer people who had ACI than microfracture needed a second repair or a knee replacement. The Assessment Group further noted that this implied that a second knee replacement would be delayed or averted.
- 4.37 The Assessment Group commented that the limitations in the economic analyses included uncertainties in the long term (beyond the period covered by the trials), including the treated natural history of disease and quality-of-life data. It stated that longer-term data from the ACTIVE trial may provide useful information in the future.

## **5 Consideration of the evidence**

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of autologous chondrocyte implantation (ACI), having considered evidence on the nature of articular cartilage defects and the value placed on the benefits of ACI by people with the condition, those who

represent them, and clinical experts. It also took into account the effective use of NHS resources.

## ***Clinical effectiveness***

### **Clinical practice and comparators**

- 5.1 The Committee considered the treatment pathway for the repair of symptomatic cartilage defects of the knee. The Committee heard from clinical experts that people with isolated condyle lesions who are considered for ACI, microfracture or mosaicplasty must have tried, and their condition not have adequately responded to, best supportive care, including physiotherapy. The Committee heard that in people for whom best supportive care has been inadequately effective, the choice between ACI, microfracture and mosaicplasty depends on lesion size, prior treatment, age, BMI, and condition of the cartilage. The Committee heard from the clinical experts that there is variation in clinical practice in the use of ACI in the NHS because the technology is not recommended by NICE. It also heard that microfracture is the most common procedure used for the repair of isolated cartilage lesions. The clinical experts advised that for people who have inadequate relief from either primary ACI or microfracture, other interventions such as mosaicplasty, debridement and lavage, osteotomy, further physiotherapy, and secondary repairs with ACI or microfracture were considered; total and partial knee replacement are used later in the treatment pathway if the damage to the cartilage leads to advanced osteoarthritis.
- 5.2 The Committee considered the relevant comparators for ACI presented in the company submissions and the Assessment Report. It noted that microfracture was considered to be the most relevant comparator and that osteotomy, knee replacement or best supportive care were not included as comparators, which was not

in accordance with the final appraisal scope. The Committee heard from clinical experts that there are currently no UK or internationally accepted treatment guidelines on how and when to treat cartilage lesions, and that it was difficult to specify the most appropriate treatment choice based on lesion size alone. However, it heard that, in general, in clinical practice the preferred treatment choice for smaller lesions was microfracture but that ACI and mosaicplasty were also used, while for larger lesions it heard that the preferred treatment choice was ACI, but that microfracture was also commonly used for a range of defect sizes. The Committee noted contradictory views on the use of mosaicplasty: the Assessment Group stated that mosaicplasty appeared to be little used in clinical practice, whereas a clinical expert stated that mosaicplasty would be the only available alternative to microfracture in many institutions because there was no general access to ACI. The Committee did not consider best supportive care (including physiotherapy) to be a relevant comparator because the Committee heard that best supportive care had already failed by the time clinicians consider ACI. The Committee considered that knee replacement was also not an appropriate comparator because clinicians rarely offered knee replacements to people who they would consider for ACI. It concluded that the choice of therapy between ACI, microfracture, mosaicplasty and osteotomy was made on an individual basis decided between clinician and patient, but that microfracture is the most relevant comparator for most people.

### **Nature of clinical effectiveness evidence**

- 5.3 The Committee was aware that ACI had been recommended only in the context of clinical trials in NICE's previous technology appraisal guidance on [the use of autologous chondrocyte implantation for the treatment of cartilage defects in the knee joints](#) because evidence on long-term clinical effectiveness for the

technology was lacking at the time of the appraisal. The Committee considered the quality of clinical trial evidence since the last appraisal on the efficacy of ACI in people with symptomatic cartilage defects in the knee. It noted 3 small studies with relatively short follow-up: Basad et al. (2010), a controlled trial with 60 patients and the SUMMIT trial with 144 patients both comparing MACI with microfracture, and the TIG/ACT trial with 118 patients comparing ACI-P using characterised chondrocytes with microfracture. It further noted that the ongoing ACTIVE trial with 390 patients compares several forms of ACI with standard treatment, that this study has an intended follow-up of 10 years, and that no results for this study have been published. The Committee considered the ACTIVE trial to be important, noting that it is the largest study among the trials with a pragmatic control group but that the final results were yet to be reported. The Committee heard from the clinical experts that many of the outcomes used in clinical trials, including the Lysholm, Tegner and Cincinnati scores, were not regularly used in clinical practice and some were of limited relevance to the general population with cartilage defects. For example, the Tegner score was designed to test performance in populations including national level competitive athletes and may therefore not distinguish outcomes adequately in the general population with lower physical performance levels. The Committee heard from the clinical experts that the Knee injury and Osteoarthritis Outcome Score (KOOS) was designed for people with cartilage injuries and is sometimes used in clinical practice. Clinical experts noted that, although a 10-point improvement in KOOS represents a clinically important difference in the KOOS response, clinicians judge the effectiveness of a person's procedure based on the person's own assessment. The Committee concluded that, among the outcomes in the trials, the KOOS score was the most appropriate on which to assess the clinical

effectiveness of ACI repair. The Committee further concluded that, although there is more clinical-effectiveness data than at the time of the previous NICE technology appraisal guidance on [the use of autologous chondrocyte implantation for the treatment of cartilage defects in the knee joints](#), the evidence base for the technology is still emerging.

### **Clinical-effectiveness results**

5.4 The Committee noted that there was evidence suggesting greater clinical effectiveness of both MACI and ChondroCelect compared with microfracture in the short term, but that the improvements with ChondroCelect after 5 years in KOOS, number of treatment failures and health-related quality of life (SF-36) were not statistically significant. By contrast, the Committee noted that the ACTIVE trial showed a statistically significant effect only after 5 years, and that the data reported by the investigators were limited. The Committee heard that the clinical experts differed with respect to how effective they perceived ACI to be compared with microfracture. The Committee heard that this may in part reflect a clinician's experience and preference. When asked to judge the clinical effectiveness of ACI, clinical experts stated that there was some evidence to show that ACI is clinically effective, but also stated that this evidence was not definitive. They also stated that, although ACI, microfracture, and mosaicplasty were probably clinically effective, evidence was lacking for the natural history of lesions treated by debridement and lavage. The clinical experts stated that some people were willing to limit their activity rather than have surgery, particularly those not involved in competitive sport. The Committee concluded that there was uncertainty in the short term clinical effectiveness of ACI although in trials ACI appears to improve symptomatic relief (based on the KOOS score).

5.5 The Committee considered whether there was evidence to demonstrate that ACI works better than microfracture in the long-term. The Committee noted that it was presented with no clinical effectiveness data beyond 5 years (although later data from the ACTIVE trial were used in the cost-effectiveness section). It further noted that there was evidence of superior clinical effectiveness of ACI compared with microfracture at up to 5 years follow-up in the ACTIVE trial. The Committee heard from OsCell that these results were provisional, and reflected a series of cross-sectional assessments. The analysis, therefore, could not account for censoring, including informative censoring. Moreover, the Committee considered it possible that, because of the open-label design, people having ACI having been advised of the longer rehabilitation time compared to microfracture may have better adhered to rehabilitation in the hope of promised long-term benefits. In addition, the Committee heard various possible observations as to why ACI would be better in the medium term, but not the short term, including that ACI has a longer rehabilitation period compared with microfracture because, over time, the chondrocytes become more organised, the tissue matures, the cartilage remodels and symptoms improve. The Committee heard from clinical experts that microfracture was associated with poorer outcomes than ACI in the long term because microfracture can damage underlying bone that can then grow into the cartilage. Clinical experts commented that some people prefer the option of microfracture because of its shorter rehabilitation period (for example, if the person wanted to return to normal activities more quickly), but that people who are involved in competitive sports tended to prefer the option of ACI because the results were likely to last longer. However, the Committee concluded the MACI and ChondroCelect trials had generated positive short-term data that were inconsistent with these observations. The Committee agreed

that, although there was additional data on the effectiveness of ACI since the previous guidance on [the use of autologous chondrocyte implantation for the treatment of cartilage defects in the knee joints](#), there were shortcomings associated with the medium-term evidence and insufficient long-term evidence to support a conclusion on the long-term effectiveness of ACI.

### **Clinical effectiveness of different forms of ACI**

5.6 The Committee considered whether any evidence supported differences in the clinical effectiveness between the 3 ACI interventions. The Committee was aware that the marketing authorisations of ChondroCelect and MACI differed in the stated lesion size. The clinical experts explained that these resulted from different trial inclusion criteria, and that in clinical practice the choice of ACI intervention, with some exceptions, was independent of lesion size. The Committee noted that the indirect comparisons of ACI-P and MACI did not show statistically significant differences between different ACI technologies, but agreed that the included trials may have been too small to detect differences. The Committee heard from the clinical experts that there was little evidence to suggest that the forms of ACI differ in their clinical effectiveness. The Committee considered whether any evidence supported characterised cells (used in the Chondrocyte and MACI products) as resulting in better clinical outcomes than ‘traditional’ cells. The Committee concluded that, although different experts may prefer one type of ACI over another (for example, because they have more experience with it), on the basis of the indirect comparison and the testimony of clinical experts the evidence did not show a difference between the alternative forms of ACI.

### **Evidence for potential subgroups**

5.7 The Committee considered whether there are any subgroups of people for whom ACI would be particularly suitable. The Committee

noted that the clinical experts could not identify characteristics of people whose condition might respond particularly well. The Committee agreed that it would not be appropriate to specify a subgroup based on age (associated with osteoarthritis), or high BMI (associated with joint load and poor outcomes). The Committee considered the evidence for whether ACI was more effective in people with shorter duration of symptoms. It noted that a predefined subgroup analysis of the TIG/ACT trial wherein ACI was (even) more effective in people with a symptom duration of less than 3 years. However, the Committee noted that, despite randomisation, there were differences in patient characteristics between the 2 groups that may confound the differences in outcomes. The Committee considered whether there was evidence to suggest that ACI was more effective than its comparators in lesions of a specific size. It noted that the claimed advantages of ACI over microfracture in its use for larger lesions was not supported by the data from a study by Minas and colleagues (2009). The Committee concluded that there was not sufficient evidence to identify a subgroup for whom ACI would be more clinically effective compared with the population defined in the scope.

## ***Cost effectiveness***

### **Economic models**

5.8 The Committee considered the economic models from the company for ChondroCelect and the Assessment Group and noted that they had broadly similar structures. Both used a Markov health-state transition model structure that allowed for ACI or microfracture, both temporary and permanent success, which in turn predicted the longer-term probability of knee replacement. The Committee commented that the models differed in how they defined treatment failure. It noted that the ChondroCelect model

defined treatment failure according to whether a person had another therapy in the trial, using time-to-treatment failure as a proxy for clinical effectiveness. The Committee understood that this implicitly assumed that everyone who did not have a subsequent therapy was a success, and agreed that this was likely to overestimate considerably the time spent in the successful primary repair state. The Committee noted that the Assessment Group's model defined treatment failure by a composite of time-to-treatment failure, and lack of response, measured by KOOS. The Committee agreed that the Assessment Group definition of response was likely to disadvantage microfracture because of the lower rate of KOOS response compared with ACI. The Committee noted the base-case ICERs for ACI compared with microfracture in the company and Assessment Group models, which were approximately £7000 and £16,000 per QALY gained respectively. However, the Committee concluded that neither definition of response used in the 2 models was ideal and that this critical variable resulted in different pathways and assumptions and, ultimately, led to significant uncertainty in the cost-effectiveness results.

- 5.9 The Committee noted that the Assessment Group's model allowed for a second repair with either ACI or microfracture, whereas the ChondroSelect model allowed for a second repair only with microfracture. It heard from the clinical expert that, in general, clinicians do not consider microfracture again in people for whom microfracture has previously failed. The Committee considered whether the treatment sequences (ACI or microfracture as either a primary or secondary repair) and the downstream treatments (partial or total knee replacement) in the submitted models reflect current clinical practice. The Committee heard from the clinical experts that in clinical practice total knee replacement is considered a 'salvage treatment' (particularly in people younger than 55 years) when people have exhausted all other options. The Committee

heard that clinicians often perform an osteotomy, debridement and lavage, or a second repair before considering doing a knee replacement. The Committee concluded that the models did not accurately reflect the treatment pathway in clinical practice but that the impact of using a more accurate treatment pathway on the ICERs was unknown.

### **Efficacy values in the models**

5.10 The Committee considered the clinical evidence used by the Assessment Group to estimate transition probabilities in the models. It noted that the Assessment Group's model used 3-year and 2-year data from separate trials for different forms of ACI to inform short-term and longer-term transition probabilities. The Committee concluded that it was not logical that the Assessment Group had used 3-year follow-up data from the TIG/ACT trial to estimate 1-year success rates in the model, and 2-year follow-up data from the SUMMIT trial to estimate success rates beyond 1 year in the model, particularly with 5-year data from the TIG/ACT trial available. The Committee was concerned that the 3-year data reflected the time period at which the difference between ACI and microfracture failure rates was the biggest. The Committee noted that the Kaplan–Meier curves for failure from the TIG/ACT trial converged after 3 years. This meant that by extrapolating 3-year data in its model, the Assessment Group may have overestimated the difference in failure rates between ACI and microfracture, and therefore may have favoured ACI. The Committee was also concerned that the approach used by the Assessment Group to estimate transition probabilities by annualising 3-year data may double count the number of people whose condition did not respond if they were not evenly distributed across the period, because some of them would also be captured in the 2-year data. The Committee stated that the Assessment Group's approach was likely biased against microfracture as a first repair because

microfracture resulted in more patients who were counted as non-responders at 1 year in the model, but who also continued to contribute to the probability of losing response beyond 1 year in the model. The Committee concluded that there was significant uncertainty in the extrapolation of clinical effectiveness data. It further concluded that the approach to calculating transition probabilities used by the Assessment Group was likely be optimistic toward ACI used as a first repair.

## **Second repair**

5.11 The Committee was concerned about the evidence used to estimate the effectiveness and probability of having a second procedure. It noted that in the company's base-case analysis for the ChondroCelect model, 90% of people who had ACI went on to get microfracture if needed, but only 5% of people who had microfracture went on to get a second microfracture. The Committee noted that the ICER increased considerably in the company's sensitivity analysis where half of people having either first procedure were assumed to have a microfracture as a second repair (see section 4.21). The Committee also noted that both models used different assumptions on the efficacy of the second repair, with the Assessment Group assuming the same efficacy as the primary repair, and the model for ChondroCelect assuming a 50% reduction in the efficacy of a second repair compared with a first repair. It heard from clinical experts that a second repair would generally be expected to be less effective than a first repair, but was aware that there was limited evidence on the efficacy of a second repair. The Committee noted that the Assessment Group's review of the literature had concluded that people with previous repairs (particularly microfracture) had poorer outcomes after ACI than people who had not had a previous repair, but that this decreased efficacy was not quantified. It heard from a clinical expert that this may be because patients who have had prior

surgery are a different group to those presenting early with limited sized chondral damage and that they would have a poor outcome that is unrelated to their prior surgery. The Committee concluded that the assumptions relating to second repairs affected the ICER, but that there was considerable uncertainty about the probability of having a second procedure and the clinical effectiveness of the second procedure.

- 5.12 The Committee was concerned about the logical inconsistencies within the transition probabilities used by the Assessment Group in which a second repair could be more effective than a first repair. However, after the Assessment Group demonstrated that this had a negligible impact on the ICER (see section 4.35); the Committee concluded that it did not need to pursue this issue further.

#### **Number of people having a total knee replacement in the model**

- 5.13 The Committee was concerned about the assumption made in the ChondroCelect model that a person of any age could get a total knee replacement following the failure of a second repair. It understood from the clinical experts that, in clinical practice, surgeons consider total knee replacement as a last resort, and only for older people, whereas younger people tended to be offered alternative procedures such as mosaicplasty, debridement and lavage, osteotomy or further ACI repairs. The Committee also understood that the ChondroCelect model included the possibility that a person could die during, or because of, a total knee replacement. The Committee therefore considered it inappropriate to model mortality benefits derived from younger people avoiding total knee replacement surgery. The Committee heard from the company that manufactures ChondroCelect, that it had explored in a sensitivity analysis the assumption that total knee replacement was only done in people aged 55 years or older which increased the ICER from approximately £7000 to £12,000 per QALY gained.

The Committee also heard from the company that the ICER increased to around £18,000 when the option of a total knee replacement was removed entirely from the model. The Committee concluded that the ICERs were sensitive to the assumptions around total knee replacement in the model and that the ChondroCelect model overestimated the benefit of ACI, both in offsetting costs and life years lost, associated with the knee replacements. .

- 5.14 The Committee heard from the clinical experts that literature-based estimates of the rates of knee replacement surgery vary widely in people with cartilage damage. The Committee also noted that there was uncertainty in the effectiveness of ACI compared with microfracture on the likelihood of subsequent total knee replacement. The Committee concluded that the variation around the probability of knee replacement in people with previous cartilage repair made it impossible to establish the most plausible estimates to use in modelling.

### **Costs of the procedure**

- 5.15 The Committee noted the costs associated with cell harvesting (first ACI procedure) and cell implanting (requiring a second procedure) varied between the Assessment Group model, the ChondroCelect model, and the OsCell analysis. The Committee discussed the appropriate costs of the 2 procedures and noted that the Assessment Group had assumed both procedures would be done as day cases, and derived the costs from the literature for both procedures. It heard from a clinical expert that most people would have both the first and second ACI procedures as day cases. The company that manufactures ChondroCelect also agreed with the day-case costs chosen by the Assessment Group. The Committee noted that the day-case cost of the first procedure used by the Assessment Group was £710, although it noted that a cost of £870

using the Healthcare Resource Groups (HRG) code HB25F would have been more appropriate. The Committee agreed that the HRG code HB22C would reflect the cost incurred by the NHS for the second procedure. It further noted that although the day-case procedure reflects clinical practice, there was no outpatient tariff for a day-case procedure using HB22C and therefore the only tariff available was a cost of £2396. The Committee noted that OsCell used the HRG code HR06A, which it stated was not appropriate for implanting cells because it reflects open major procedures and not arthroscopic surgery. The Committee concluded that the Assessment Group's estimate for the cost of harvesting cells was reasonable, but for implanting cells the code HB22C most closely reflected the price incurred by the NHS at a cost of £2396.

### **Cost of the cells**

5.16 The Committee considered the most appropriate costs of producing and supplying cells. It noted that in the base-case analyses the Assessment Group model and the ChondroSelect model had assumed a cost of £16,000, which was based on the approximate list prices of ChondroSelect and MACI. However, the Committee understood from the Assessment Group that there are confidential discounts sometimes provided to the NHS by the companies, making the real cost difficult to evaluate. The Committee noted that the OsCell submission had estimated a production cost of the cells of £4125. The Committee heard from a representative of OsCell that the cost of cells included the cost of materials and staff time, but not the costs of overheads. The Committee therefore considered that OsCell had underestimated its cell costs, and that the true cost may approach that of MACI and ChondroSelect. The Committee concluded that, although the cost to the NHS of providing the cells for ACI was somewhat uncertain, the cost estimate used by the Assessment Group and for the

ChondroCelect model was reasonable for the purposes of decision-making.

### **Utility data**

- 5.17 The Committee noted that the Assessment Group in its model had adjusted the utility at year 5 and beyond from 0.82 to 0.65 for the microfracture success state, to reflect evidence that the benefit of microfracture declines after 5 years. The Committee noted that this was equivalent to assuming that microfracture has failed in all people at year 5. The Committee considered that it would have been preferable to adjust for the reduced efficacy of microfracture more explicitly by adjusting the transitions probabilities instead of the utility of the 'success' health state. The Committee concluded that reducing the utility value for microfracture after 5 years was arbitrary and inappropriately favoured ACI. The Committee noted a sensitivity analysis from the Assessment Group in which it set the utility at year 5 and beyond for the microfracture success state to 0.817, and that this increased the ICER to over £20,000 per QALY gained. The Committee therefore concluded that a more plausible approach to modelling utility would likely increase the Assessment Group's base-case ICER.
- 5.18 The Committee considered the source of utility values used in the Assessment Group and ChondroCelect models. The Committee understood that, because of the short duration of the trials, there is limited long-term data on utility values associated with either ACI or microfracture. The Committee noted that the utility values for health states associated with microfracture or ACI knee repairs in the Assessment Group and ChondroCelect models had been obtained from a study published by Gerlier et al. (2010) that compared ACI with microfracture using 5-year data from the TIG/ACT ChondroCelect trial. The Committee noted a lack of transparency in the literature with respect to the sample size, missing values and

how the authors had mapped the SF-36 data to a health utility index. The Committee considered the utility of different health states in the model and remarked that the utility value prior to surgery in both models (0.65) appeared low, particularly when compared to other chronic debilitating conditions. The Committee further noted that the pre-surgery utility values in the ACTIVE trial were even lower, although the relative changes in utility values were similar to those from the TIG/ACT trial. The Committee heard the clinical expert state that young active people may perceive cartilage injuries as particularly disabling. The clinical expert explained that the participants in the trials were young and many were competitive athletes, and therefore would not necessarily reflect the population considered for ACI in clinical practice. The Committee concluded that there was considerable uncertainty about the validity of the modelled absolute utility values used to reflect the type of person who would have ACI in England.

- 5.19 The Committee noted that in the ChondroCelect model, the company assumed that anyone who did not undergo a second procedure had a utility value equivalent to someone who had a successful first procedure and whose condition responded (using KOOS criteria). However, the Committee considered this implausible because some people who do not have a second procedure would be considered non-responders according to the KOOS criteria. The Committee stated that a weighted utility value for people whose condition responded or did not respond to a first procedure (using KOOS criteria) would have been more plausible. The Committee noted that the Assessment Group used a utility value for people who moved to the no-further-repair health state of 0.69, which reflected people who had some benefit from the first repair and so did not have a utility as low as before the first procedure. The Committee noted that using more plausible assumptions for the utility of the no further repair health state

increased the ICER from around £15,000 to around £20,000 per QALY gained (see section 4.35). The Committee concluded that there was uncertainty in estimating utility values for people who did not have a second repair, and that the base case approaches used by the company that manufactures ChondroCelect and the Assessment Group favoured ACI.

### **Time horizon**

5.20 The Committee noted that reducing the time horizon considerably increased the ICER in the ChondroCelect model (using a time horizon of 5 years; see section 4.21) and moderately increased the ICER in the Assessment group model (see section 4.34). The Committee understood that the majority of costs of ACI are incurred in the first few years, and the modelled benefits from ACI are not expected until later. The Committee noted that OsCell's analysis for traditional ACI used data collected at 8 years, but that this was (as acknowledged by the company) only a 'crude' analysis that did not use a cost effectiveness model and was based on interim data from ACTIVE using a small sample size. The Committee concluded that the lifetime horizon was preferable because it captured all of the costs and consequences of treatment, but the lack of long-term data with which to populate a model generated large uncertainties.

### **Innovation**

5.21 The Committee noted that the companies all considered ACI to be innovative, mainly for reasons related to the technical detail of the procedures. The Committee agreed that ACI, albeit not new, is technically innovative, but that in the context of a technology appraisal, innovation needs to be judged by the benefit for patients, and that with the current uncertainties in the clinical effectiveness, it was not possible to conclude that these technologies can be considered innovative.

## **Conclusion**

- 5.22 The Committee considered that there was no ICER available that included the assumptions that the Committee considered plausible, and that several key parameters in the Assessment Group model and ChondroCelect model could not be populated with evidence-based data. Despite the low base-case ICERs presented, the Committee noted that several sensitivity analyses using more plausible assumptions individually increased the ICER, for example, reducing the probability of total knee replacement in the ChondroCelect model (see section 5.13), or using more appropriate utility values in the Assessment Group's model (see section 4.35). The Committee noted that the key drivers determining the ICERs were procedural and cell costs and utility values (see section 4.34), both of which were associated with uncertainty. The Committee noted the substantial structural uncertainty in the economic models, which did not reflect the treatment pathway in UK clinical practice (see sections 5.8 and 5.9). The lack of long-term data on the relative effect of ACI compared with microfracture on the probability of knee replacement later in life added further uncertainty. Therefore, the Committee was not persuaded that ACI was proven to be a cost-effective treatment. Moreover, the Committee considered that the available data did not robustly support that ACI was better than other treatments (see sections 5.4 and 5.5).
- 5.23 The Committee therefore recommended that, because the clinical effectiveness and cost-effectiveness of ACI remains uncertain, ACI should not be recommended for routine use in the NHS unless it is part of existing or new clinical studies. The Committee noted that these studies should generate robust outcome data and include both interventional and observational studies.

**Summary of Appraisal Committee’s key conclusions**

TAXXX	Appraisal title:	Section
<b>Key conclusion</b>		
<p>Autologous chondrocyte implantation is recommended only in research for repairing symptomatic articular cartilage defects of the knee.</p> <p>The Committee considered that the available data did not robustly support that ACI was more effective than other treatments. In particular, the lack of long-term data on the relative effect of ACI compared with microfracture added uncertainty.</p> <p>No ICER was available that included the assumptions that the Committee considered plausible, and several key parameters in the Assessment Group model and ChondroCelect model could not be populated with evidence-based data. Despite the low base-case ICERs presented, the Committee noted that several sensitivity analyses using more plausible assumptions individually increased the ICER.</p> <p>The Committee noted that these studies should generate robust outcome data to measure the long-term benefits of autologous chondrocyte implantation and include both interventional and observational studies.</p>	<p>1.1</p> <p>5.21</p> <p>5.22</p> <p>5.23</p>	
<b>Current practice</b>		
<p>Clinical need of patients, including the availability of alternative treatments</p>	<p>There are currently no UK or internationally accepted treatment guidelines on how and when to treat cartilage lesions, and it is difficult to specify the most appropriate treatment choice based on lesion size alone. However, in general, in clinical practice the preferred treatment choice for smaller lesions was microfracture but that ACI and mosaicplasty were also used, while for larger lesions it heard that the preferred treatment choice was ACI, but that microfracture was also commonly used for a range of defect sizes.</p> <p>The Committee did not consider best supportive care or knee replacement to be relevant comparators for ACI and concluded that the choice of therapy between ACI, microfracture, mosaicplasty and osteotomy was made on an individual basis decided between clinician and patient, but that microfracture is the most relevant comparator for most people.</p>	<p>5.2</p>

<b>The technology</b>		
Proposed benefits of the technology  How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The Committee heard various possible observations as to why ACI would be better than microfracture in the medium term, but not the short term, including that ACI has a longer rehabilitation period compared with microfracture but because, over time, the chondrocytes become more organised, the tissue matures, the cartilage remodels and symptoms improve potentially giving longer lasting success.  It was not possible to conclude that these technologies can be considered innovative.	5.5
What is the position of the treatment in the pathway of care for the condition?	The Committee heard from clinical experts that people with isolated condyle lesions who are considered for ACI, microfracture or mosaicplasty must have tried, and their condition not have adequately responded to, best supportive care, including physiotherapy. The Committee heard that in people for whom best supportive care has been inadequately effective, the choice between ACI, microfracture and mosaicplasty depends on lesion size, prior treatment, age, BMI, and condition of the cartilage. The Committee heard from the clinical experts that there is variation in clinical practice in the use of ACI in the NHS because the technology is not recommended by NICE.	5.1
Adverse reactions	No specific considerations.	N/A
<b>Evidence for clinical effectiveness</b>		
Availability, nature and quality of evidence	The key clinical effectiveness evidence for ChondroCelect came from the randomised controlled trial, TIG/ACT/01/2000. For MACI it came from 2 randomised controlled trials, SUMMIT and Basad et al. (2010). For traditional ACI, the key clinical effectiveness evidence came from the randomised controlled trial, ACTIVE.  The Committee considered the ACTIVE trial	5.3

	<p>to be important but noted it was ongoing with an intended follow-up of 10 years, and that no results for this study had been published. The Committee concluded that, although there is more clinical-effectiveness data than at the time of the previous NICE technology appraisal guidance on the use of ACI for the treatment of cartilage defects in the knee joints, the evidence base for the technology is still emerging.</p>	
<p>Relevance to general clinical practice in the NHS</p>	<p>The Committee heard from the clinical experts that many of the outcomes used in clinical trials were not regularly used in clinical practice and some were of limited relevance to the general population with cartilage defects. The Committee concluded that the KOOS score was the most appropriate on which to assess the clinical effectiveness of ACI repair.</p>	<p>5.3</p>
<p>Uncertainties generated by the evidence</p>	<p>The Committee noted 3 small studies with relatively short follow-up (Basad et al. [2010], the SUMMIT and the TIG/ACT trials). It considered the ongoing ACTIVE trial, noting that it is the largest study among the trials but that the final results were yet to be reported. The Committee agreed there were shortcomings associated with the medium-term evidence and insufficient long-term evidence to support a conclusion on the long-term effectiveness of ACI.</p> <p>The Committee heard from OsCell that the results from ACTIVE were provisional, and reflected a series of cross-sectional assessments. The analysis, therefore, could not account for censoring, including informative censoring. The Committee considered it possible that, because of the open-label design, people having ACI having been advised of the longer rehabilitation time compared to microfracture may have better adhered to rehabilitation in the hope of promised long-term benefits.</p>	<p>5.3</p> <p>5.5</p>

Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The Committee concluded that there was not sufficient evidence to identify a subgroup for whom ACI would be more clinically effective compared with the population defined in the scope	
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee concluded that there was uncertainty in the short term clinical effectiveness of ACI although in trials ACI appears to improve symptomatic relief (based on the KOOS score).  The Committee agreed there were shortcomings associated with the medium-term evidence and insufficient long-term evidence to support a conclusion on the long-term effectiveness of ACI.	5.4  5.5
<b>For reviews (except rapid reviews):</b> How has the new clinical evidence that has emerged since the original appraisal (TAXXX) influenced the current (preliminary) recommendations?	The Committee agreed that, although there was additional data on the effectiveness of ACI since the previous guidance on <a href="#">the use of autologous chondrocyte implantation for the treatment of cartilage defects in the knee joints</a> , there were shortcomings associated with the medium-term evidence and insufficient long-term evidence to support a conclusion on the long-term effectiveness of ACI.	5.5
<b>Evidence for cost effectiveness</b>		
Availability and nature of evidence	The ChondroCelect submission presented a de novo Markov economic model. The Assessment Group also constructed a Markov model.	4.20  4.27

<p>Uncertainties around and plausibility of assumptions and inputs in the economic model</p>	<p>The Committee concluded that neither definition of response used in the ChondroCelect or Assessment Group models were ideal.</p>	5.8
	<p>The Committee concluded that the models did not accurately reflect the treatment pathway in clinical practice.</p>	5.9
	<p>The Committee noted that the Assessment Group’s model used 3 year and 2 year data from separate trials for different forms of ACI to inform short-term and longer-term transition probabilities.</p>	5.10
	<p>The Committee heard that literature-based estimates of the rates of knee replacement surgery vary widely in people with cartilage damage and this made it impossible to establish the most plausible estimates to use in modelling.</p>	5.11
	<p>The Committee concluded that there was significant uncertainty in</p> <ul style="list-style-type: none"> <li>• the extrapolation of clinical effectiveness data.</li> <li>• the probability of having a second procedure and the clinical effectiveness of the second procedure.</li> <li>• the validity of the modelled absolute utility values used to reflect the type of person who would have ACI in England.</li> <li>• in estimating utility values for people who did not have a second repair.</li> </ul>	5.14
		5.18
	5.19	

<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>The Committee noted that the utility values for health states associated with microfracture or ACI knee repairs in the Assessment Group and ChondroCelect models had been obtained from a study published by Gerlier et al. (2010) using 5 year data from the TIG/ACT ChondroCelect trial, and that this study lacked transparency with respect to the sample size, missing values and how the authors had mapped the SF 36 data to a health utility index.</p>	<p>5.18</p>
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>Cost effectiveness analyses were not carried out for specific subgroups.</p>	
<p>What are the key drivers of cost effectiveness?</p>	<p>The main driver of cost effectiveness for the ChondroCelect model was the time to failure of the first repair.</p> <p>Based on its sensitivity analyses, the Assessment Group stated that the key drivers in the base case were the cost of cells for ACI and how long patients benefitted from ACI or microfracture.</p> <p>The Committee noted that the key drivers determining the ICERs were procedural and cell costs and utility values.</p>	<p>4.21</p> <p>4.36</p> <p>5.21</p>

<p>Most likely cost-effectiveness estimate (given as an ICER)</p>	<p>The Committee considered that there was no ICER available that included the assumptions that the Committee considered plausible, and that several key parameters in the Assessment Group model and ChondroCelect model could not be populated with evidence-based data.</p>	<p>5.21</p>
<p><b>For reviews (except rapid reviews):</b> How has the new cost-effectiveness evidence that has emerged since the original appraisal (TAXXX) influenced the current (preliminary) recommendations?</p>	<p>The Committee recommended that, because the clinical effectiveness and cost-effectiveness of ACI remains uncertain, ACI should not be recommended for routine use in the NHS unless it is part of existing or new clinical studies.</p>	<p>5.22</p>
<p><b>Additional factors taken into account</b></p>		
<p>Patient access schemes (PPRS)</p>	<p>No patient access schemes were included.</p>	
<p>End-of-life considerations</p>	<p>Not relevant</p>	
<p>Equalities considerations and social value judgements</p>	<p>No equalities issues relevant for the appraisal were raised</p>	

## 6 Proposed recommendations for further research

- 6.1 Research is ongoing in a variety of areas. The largest study is the ACTIVE trial comparing ACI with alternative treatment. The final 10-year outcome from this study is expected to be available in 2021. The ongoing SUMMIT Extension study has completed 1 year of a planned 3-years follow-up. The Basad et al. (2010) randomised controlled trial comparing MACI with microfracture published 2-year data, and published 5-year follow-up data from this trial are anticipated within 12 months. The registry-based cohort study (TGX001-2011) collecting data in Belgium and the Netherlands cohort study based on a registry (TGX001-2011) is an ongoing open label, non-interventional study in which efficacy and safety data is collected from routine clinical follow-up in a 'real-life' settings in Belgium and the Netherlands. OsCell report that the data from an Arthritis Research UK-funded study of ACI (at the Robert Jones and Agnes Hunt Orthopaedic Hospital) compared with microfracture or debridement, that is specifically looking at the rate of development of osteoarthritis, should be available within 12 months.
- 6.2 As discussed in Section 4, evidence on the benefits of ACI compared with other treatments is lacking. Key issues relate to medium- to long-term outcomes, including the onset of osteoarthritis, the need for arthroplasty and knee replacement, and the durability of different types of chondral repair. Systematic collection of information on long-term outcomes is needed for all patients treated with ACI, for example through the development of national registries.
- 6.3 Evidence is lacking to support the assumption that use of surgical intervention results in a long-term cartilage repair that cannot be

achieved by other means. Further research is recommended to compare chondrocyte implantation techniques, mosaicplasty and microfracture with conservative treatment, for example, sham (placebo) procedure, lavage and debridement, or intensive physiotherapy that reflects the rehabilitation following ACI.

## 7 Related NICE guidance

Details are correct at the time of consultation and will be removed when the final guidance is published. Further information is available on the [NICE website](#).

### Published

- [Partial replacement of the meniscus of the knee using a biodegradable scaffold](#). NICE interventional procedure guidance 430 (2012)
- [Mosaicplasty for knee cartilage defects](#). NICE interventional procedure guidance 162 (2006)
- [Autologous chondrocyte implantation for the treatment of cartilage defects in the knee joints](#). NICE technology appraisal guidance 89 (2005); this guidance updated and replaced NICE technology appraisal 16 (2000)

## 8 Proposed date for review of guidance

- 8.1 NICE proposes that the guidance on this technology is considered for review by the Guidance Executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Dr Amanda Adler  
Chair, Appraisal Committee  
March 2015

## **9 Appraisal Committee members, guideline representatives and NICE project team**

### **9.1 *Appraisal Committee members***

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

#### **Dr Amanda Adler (Chair)**

Consultant Physician, Addenbrooke's Hospital

#### **Professor Ken Stein (Vice Chair)**

Professor of Public Health, University of Exeter Medical School

#### **Professor Keith Abrams**

Professor of Medical Statistics, University of Leicester

#### **Dr Ray Armstrong**

Consultant Rheumatologist, Southampton General Hospital

#### **Dr Jeff Aronson**

Reader in Clinical Pharmacology, University Department of Primary Health Care, University of Oxford

**Professor John Cairns**

Professor of Health Economics Public Health and Policy, London School of Hygiene and Tropical Medicine

**Mr Matthew Campbell-Hill**

Lay Member

**Mr Mark Chapman**

Health Economics and Market Access Manager, Medtronic UK

**Dr Lisa Cooper**

Echocardiographer, Stockport NHS Foundation Trust

**Professor Daniel Hochhauser**

Consultant in Medical Oncology, UCL Cancer Institute

**Dr Neil Iosson**

Locum General Practitioner

**Mrs Anne Joshua**

NHS 111 Pharmacy Lead, Patients and Information, NHS England

**Dr Sanjay Kinra**

Clinical Lecturer, University of Warwick

**Dr Miriam McCarthy**

Consultant, Public Health, Public Health Agency, Northern Ireland

**Dr Peter Norrie**

Principal Lecturer in Nursing, DeMontfort University

**Professor Stephen Palmer**

Professor of Health Economics, Centre for Health Economics, University of York

**Dr John Pounsford**

Consultant Physician, Frenchay Hospital, Bristol

**Dr Danielle Preedy**

Lay Member

**Mr Cliff Snelling**

Lay Member

**Ms Marta Soares**

Research Fellow, Centre for Health Economics, University of York

**Professor Andrew Stevens**

Professor of Public Health, Department of Public Health and Epidemiology,  
University of Birmingham

**Dr Nerys Woolacott**

Senior Research Fellow, Centre for Health Economics, University of York

## **9.2**      ***NICE project team***

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

### **Chris Chesters**

Technical Lead

### **Eleanor Donegan**

Technical Adviser

### **Jeremy Powell**

Project Manager

## 10 Sources of evidence considered by the Committee

A. The assessment report for this appraisal was prepared by Warwick

Evidence:

- Mistry H, Shyangdan D, Clar C. et al., Autologous chondrocyte implantation in the knee, December 2014

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, assessment report and the appraisal consultation document (ACD). Organisations listed in I, II and III were also invited to make written submissions and have the opportunity to appeal against the final appraisal determination.

I. Companies:

- Aaastrom Biosciences
- Robert Jones & Agnes Hunt Orthopaedic & District Hospital NHS Trust (RJAH)
- Swedish Orphan Biovitrum AB (Sobi)

II. Professional/specialist and patient/carer groups:

- Primary Care Rheumatology Society
- Royal College of Physicians

III. Other consultees:

- Department of Health
- NHS England
- Welsh Government

IV. Commentator organisations (without the right of appeal):

- Cell Therapy Catapult
- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland

C. The following individuals were selected from clinical specialist and patient expert nominations from the consultees and commentators. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on autologous chondrocyte implantation by attending the initial Committee discussion and/or providing written evidence to the Committee. They are invited to comment on the ACD.

- Mr John Keating, Consultant Orthopaedic Surgeon, Royal Infirmary of Edinburgh, nominated by Healthcare Improvement Scotland – clinical expert
- Professor Martyn Snow, Consultant Orthopaedic Surgeon, The Royal Orthopaedic Hospital, Birmingham, nominated by Sobi – clinical expert

D. Representatives from the following companies attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Aastron Biosciences
- Robert Jones & Agnes Hunt Orthopaedic & District Hospital NHS Trust (RJAH)
- Swedish Orphan Biovitrum AB (Sobi)