NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

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

This premeeting briefing is a summary of:

- the evidence and views submitted by the companies, the consultees and their nominated clinical experts and patient experts and
- the assessment report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document is a summary of the information available before comments on the assessment report have been received.

Key issues for consideration

Clinical effectiveness evidence

- The NICE scope lists as interventions 3 different autologous chondrocyte implantation (ACI) technologies, ChondroCelect (TiGenix), matrix applied characterised autologous cultured chondrocyte implant (MACI; Vericel Corporation), and traditional ACI. The scope lists a number of comparators: microfracture, mosaicplasty, osteotomy, knee replacement and best supportive care. The assessment group (AG) considered microfracture to be the main comparator for any size of lesion. It considered mosaicplasty to be a comparator but noted that it is now in limited use for small defects only. It did not consider the other comparators listed in the scope to be appropriate comparators (see the

comparators section of the PICO table in section 3.1 for more details). What are the most clinically appropriate comparators?

- Second generation ACI-C (the 'C' refers to the use of a collagen cap) and third generation ACI-M (the 'M' refers to the use of a matrix/collagen membrane) are used in clinical practice in the UK, but have developed from the earlier (first generation) versions of ACI-P (the 'P' refers to the use of a periosteum cap). The longest term data (for example, the TIG/ACT trial and the early years of the ACTIVE trial) comes from the use of ACI-P which has been superseded in clinical practice in the UK. Is there any difference in the clinical efficacy of different generations of ACI, and what are the Committee's views for how it should interpret potential differences?
- A number of studies suggest that ACI is less successful in people who have had previous microfracture than if it is done as first repair, because microfracture damages the subchondral bone. Although not suggested in the final scope of the appraisal, should the sequencing of different procedures for cartilage repair (for example microfracture followed by ACI) be considered in the guidance recommendations?

Cost effectiveness evidence

- For the economic analysis the AG have treated ACI as a class rather than assessing the cost effectiveness of the 3 separate interventions. Is this appropriate or is there evidence to suggest that the interventions have clinically different outcomes that would have to be modelled separately?
- There were variations across the AG model, the ChondroCelect model and the OsCell cost effectiveness analysis in the costs assumed for the 2 ACI procedures. The costs assumed for the first procedure were £710 for the AG model, £722 for the ChondroCelect model, and £2398 for the OsCell analysis. The AG assumed the second procedure would be performed as a day case whereas the ChondroCelect model assumed it would be in an outpatient visit. Excluding the cost of the cells, the costs assumed for the second ACI procedures were £1030 for the AG model, £110 for the ChondroCelect model, and £2751 for the OsCell

analysis. What are the most appropriate procedure costs to be used in the base case analysis?

- The AG used a cell cost of £16,000 which is based on the approximate list prices of ChondroCelect and MACI. However, it is known that there are confidential discounts provided to the NHS by the manufacturers which vary by time and location. In addition, the OsCell cells are not commercially available, but the OsCell submission estimated a production cost of £4125. The AG addressed the issue of the cost of cells by sensitivity analysis. What is the most appropriate cost of cells to be used in the base case analysis?
- The utility values reported from the ACTIVE trial are [redacted] than those reported from the TIG/ACT trial of ChondroCelect (used in the base case), and the use of different utility values has a large impact on the ICER. Which source of utility values is most appropriate?
- Key limitations in the economic analyses included uncertainties with long-term treatment failure and progression rates. How does the Committee view the evidence of the long-term effectiveness of ACI and how these uncertainties have been addressed in the existing models?

1 Background: clinical need and practice

1.1 The underside of the patella, or kneecap, is covered with articular cartilage, a type of hyaline cartilage, which is found on many joint surfaces. Hyaline cartilage is normally very smooth, promoting frictionless movements of the joints and also acting as a shock absorber. The cellular component of hyaline cartilage is the chondrocyte, which is responsible for the production and maintenance of the cartilage matrix which is formed mainly from a protein called type 2 collagen. Cartilage has no blood and nerve supply, and has a limited potential for self-repair.

1.2 Cartilage damage can be caused directly by injury, various types of arthritis, or spontaneously. Cartilage damage may also arise because of knee instability or abnormal loading, for example after a ligament injury or

damaged meniscal cartilages. Obesity may also affect knee cartilage. In young people the most common cause of hyaline cartilage damage is sporting injuries. Symptoms associated with the loss of hyaline cartilage include knee pain, knee swelling, joint locking (that is, where a joint becomes stuck in one position) and giving way of the joint. In addition, damage to the cartilage and surrounding tissues can lead to osteoarthritis in later life and can also lead to a requirement for total knee replacement (TKR) or partial knee replacement (PKR) surgery because of increasing pain and disability. People who undergo a knee replacement have an increased mortality risk during surgery.

1.3 It is estimated that every year in the UK, around 10,000 people are indicated for the treatment of cartilage damage. The number of people with symptomatic cartilage defects suitable for autologous chondrocyte implantation is estimated to be between 200 and 500 per year in the UK. The true incidence and prevalence of hyaline cartilage damage in knee joints is not known. This is partly because cartilage defects may arise from a variety of direct injuries, and they may also arise indirectly many months or years after a previous knee injury. In addition, people with knee symptoms that are a result of cartilage defects may present to a variety of medical practitioners, and may be evaluated with differing diagnostic approaches.

1.4 Knee injuries requiring hospital admission are associated with a significant impact on quality of life. In professional sportsmen and women, and in people who have physically demanding jobs, cartilage injuries, in addition to limiting quality of life, may lead to loss of employment. Current treatment options aim to relieve symptoms and include knee lavage with or without debridement (removal of damaged cartilage) and procedures to re-establish the articular surface. Microfracture is a common procedure used to re-establish the articular surface, which involves drilling small holes through the bone underlying the damaged area to allow the marrow cells to fill the defect. However the fibrocartilage formed is less durable

than natural hyaline cartilage, and cartilage repaired like this wears out over the years. Microfracture is normally used for lesion sizes of less than 13 cm^2. 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 can only be used for small areas of damage (less than 4 cm^2) because the transplanted sections have to come from elsewhere in the knee, usually the trochlea. Autologous chondrocyte implantation (ACI) involves the harvesting, culture and implantation of healthy cartilage cells (chondrocytes) into the area of the cartilage defect. Larger lesions and failed cartilage repair are generally managed by osteotomy (realigning of the knee) and knee replacement.

1.5 ACI comprises a series of procedures. First chondrocytes are harvested arthroscopically from the affected knee joint by a cartilage biopsy. The chondrocytes are cultured in a laboratory to increase their number and in a second surgical procedure the chondrocytes are implanted into the damaged areas of the cartilage to form a new layer of hyaline or hyaline-like cartilage. ACI is not used where there is joint instability that cannot be corrected simultaneously or where there is existing osteoarthritis.

1.6 ACI has evolved over many years. In the first generation of ACI, the cultured chondrocytes were placed in the cartilage lesion, in liquid form, and then covered with a cap made from periosteum (ACI-P) which is the tough fibrous tissue that covers bones, while in the second generation this cap was made from collagen (ACI-C). In the third generation of ACI (ACI-M) the chondrocytes are seeded on to a porcine collagen membrane which ensures a homogeneous cell distribution and avoids the risk of chondrocyte leaking from the liquid cell suspension. The branded MACI product (see section 2.4) is provided in the form of a collagen membrane in which the cultured chondrocytes have already been seeded. MACI is therefore a third generation ACI technique only. ChondroCelect is provided in the form of a vial containing the cultured chondrocytes, and,

as with traditional ACI, the cells can be used for first, second or third generation ACI. Unlike MACI, ChondroCelect and traditional ACI require a separate commercially available collagen membrane to be used for third generation ACI. Additionally, both ChondroCelect and MACI only use selected chondrocytes – this is called characterised chondrocyte implantation (this does not apply to traditional ACI). In this process, cells most likely to produce hyaline cartilage with predominantly type II collagen (rather than a less resilient fibro-cartilage which produces mainly type I collagen), are identified and selected by using a panel of biomarkers.

1.7 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 revealed a consensus for debridement and/or microfracture as a first choice treatment for full-thickness cartilage lesions of up to 3 cm^2. For the treatment of lesions larger than 3 cm^2 there was less agreement: ACI (any generation) was preferred by 33.5% of the experts, microfracture by 19% and debridement by15% and several other techniques. The most appropriate place for ACI in clinical practice has been described by the Medical Services Advisory Committee (a Committee advising the Australian health minister) for the treatment of a full thickness chondral defect surrounded by healthy cartilage in an otherwise healthy knee. Current NICE guidance (technology appraisal 89) does not recommend autologous chondrocyte implantation (ACI) for the treatment of articular cartilage defects of the knee except in the context of ongoing or new clinical studies because, at the time of the appraisal (2005), the data available (particularly long-term data) was too limited to draw conclusions about the relative cost effectiveness of ACI versus treatment alternatives. The assessment group (AG) described the potential treatment pathway that might involve ACI as follows:

- Patient has persistent pain and limitation of activities such as sport, despite symptomatic treatment and physiotherapy. Symptoms include

pain, locking, and the knee giving way, and can impair quality of life as much as osteoarthritis.

- Patient is referred to orthopaedic specialist.
- Investigations are carried out: usually an MRI scan first, then arthroscopy, and often debridement and lavage.
- A regenerative procedure is carried out, such as ACI or microfracture.

2 The technologies

ChondroCelect

2.1 ChondroCelect is used as part of an ACI procedure. The ChondroCelect product is a vial containing selected characterised viable autologous human cartilage cells at a concentration of 10,000 cells per microlitre. ChondroCelect was approved 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 randomised controlled trial that supported the marketing authorisation for ChondroCelect included patients with lesions between 1 and 5 cm^2. The summary of product characteristics does not specify one particular method of administration, but notes that the clinical data which supports the marketing authorisation is based on ChondroCelect used with a periosteal cap (first generation ACI-P). It also notes that although the clinical safety of ChondroCelect has not been evaluated with other forms of implantation, it may also be used with a collagen membrane (second generation ACI), or with a commercially available collagen membrane in which the cells are seeded prior to implantation (third generation ACI).

2.2 The ChondroCelect summary of product characteristics lists the following as the most frequently occurring adverse reactions: arthralgia (joint pain), cartilage hypertrophy, joint crepitation (popping and cracking sounds in the joint), joint effusion (abnormal amount of 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.

2.3 The list price of the ChondroCelect product is £18,301 for 1 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

2.4 MACI refers to matrix associated chondrocyte implantation. The branded MACI product is a porcine derived type I/III collagen membrane in which characterised viable autologous chondrocytes have been seeded. The implant has a density of 500,000 to 1,000,000 cells per cm^2, which is trimmed by the surgeon to the size and shape of the cartilage lesion. MACI was approved 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^2 in skeletally mature adult patients. MACI is, by definition, a third generation ACI technique.

2.5 The MACI summary of product characteristics lists the following as the most frequently occurring adverse reactions: symptomatic graft hypertrophy and graft delamination (complete or partial, possibly leading to loose bodies in the joint or graft failure). 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.

2.6 The list price quoted in the submission for the MACI product is £16,226 for 1 implant (price excluding VAT). Costs may vary in different settings because of negotiated procurement discounts.

Traditional ACI

2.7 The OsCell John Charnley Laboratory is an NHS laboratory at the Robert Jones and Agnes Hunt (RJAH) Orthopaedic Hospital in Oswestry. The facility has its own specially developed cell-culture facilities and has been providing autologous chondrocytes for use in ACI since 1997. It is the only NHS facility that currently cultures cells for use in ACI. The OsCell product is manufactured under an MHRA Manufacturing and Importation Authorisation for Investigational Medicinal Products (MIA[IMP]) licence which enables the technology to be supplied to hospitals around the UK and in Norway for use in clinical trials only. The facility has also applied for a Hospital Exemption Licence which would enable OsCell to culture the cells and supply chondrocytes for use in ACI in a hospital under the exclusive professional responsibility of a medical practitioner. The submission notes that 30 to 40 people are currently being treated with ACI each year at RJAH. Unlike ChondroCelect and MACI, the cells produced by OsCell are not characterised. OsCell has stated that they prefer to implant cultured chondrocytes under a sutured membrane (second generation ACI-C) because it is associated with cartilage with more type II collagen, but that they also seed cells into a membrane (third generation ACI-M) in patients where it is difficult to get the suturing of a membrane over cells.

2.8 The OsCell product does not have a marketing authorisation and it is therefore not commercially available. The OsCell submission states that production of cells in Oswestry cost £4125 per patient. The 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”. It is supplied as an autologous cell therapy product of 1 to 20

million cells in a sterile syringe in a volume of 0.2 to 0.6 ml of autologous serum as prescribed by the surgeon. A single dose is inserted at the time of surgery.

3 Remit and decision problem(s)

3.1 The remit from the Department of Health for this appraisal was: To appraise the clinical and cost effectiveness of autologous chondrocyte implantation within the applicable licensed indications for repairing symptomatic articular cartilage defects of the knee (to include a review of technology appraisal 89 where appropriate).

	Final scope issued by NICE	**Additional comments or specifications in the Assessment Group's protocol**
Population	Adults with a symptomatic cartilage defect (chondral defect) but without advanced osteoarthritis". The chondral defects can be on the femur, tibia or patella	No age restriction is given in the scope from NICE, but in past trials, patients had a mean age of 32, range 16 to 49, with about 60% men. In most cases, the cartilage damage was due to injury, usually from sport. The AG's model therefore considers a hypothetical cohort of 1000 patients with symptomatic articular cartilage defects of the knee with a starting age of 33 years followed from their first repair The AG noted that [redacted]
	Final scope issued by NICE	**Additional comments or specifications in the Assessment Group's protocol**
Intervention	• Characterised Chondrocyte Implantation using ChondroCelect • Matrix-applied characterised autologous cultured chondrocytes (MACI) • Traditional autologous chondrocyte implantation (currently authorised on	The technology is evolving, and the longest term data come from versions of ACI which are superseded. In examining the cost effectiveness of ACI, the AG consider the use of ACI as one class of interventions.

	hospital exemptions from the 'advanced therapy medicinal products' regulation)	
	Final scope issued by NICE	**Additional comments or specifications in the Assessment Group's protocol**
Comparators	As appropriate for lesion size: • Microfracture (marrow stimulation) • Mosaicplasty • Osteotomy (realignment of the knee) • Knee replacement • Best supportive care The interventions will be compared with each other where appropriate.	The main comparator is microfracture, for any size of lesion. Mosaicplasty is used less frequently, but remains a comparator for small lesions. The inclusion of knee replacement is inappropriate: it is not used in young people with isolated cartilage defects but rather, it is a longer-term intervention if the damage leads to advanced osteoarthritis. Osteotomy is not considered a comparator, but it may sometimes be used in combination with ACI to realign a knee. Osteotomy may feature in modelling since it can be used to postpone knee replacement in younger people. If ACI is successful, the costs of osteotomy may be avoided. Best supportive care is interpreted to be non-operative intervention, including symptomatic relief from analgesics such as paracetamol and non-steroidal anti-inflammatory agents, and rehabilitation interventions such as physiotherapy. The AG assumed that conservative, non-surgical treatments such as physiotherapy would be tried first, and so would not be a comparator, [redacted]
	Final scope issued by NICE	**Additional comments or specifications in the Assessment Group's protocol**
Outcomes	• pain	The outcome measures used in ACI

	• knee function including long-term function • rates of retreatment • activity levels, such as return to work or sport • avoidance of osteoarthritis, and knee replacement • adverse effects of treatment • health-related quality of life.	studies include; • the Lysholm score which assesses function and symptoms on a scale of 0 to 100 • the Tegner score which grades activity level on a scale from 0, disability due to knee problems, to 10, ability to take part in competitive sports at national level • the Knee Injury and Osteoarthritis Outcome Score (KOOS) assesses pain, symptoms, activities of daily living, sport and recreational activities, on a scale of 0 to 100. The commonest adverse event is failure to repair the area of damaged cartilage.

3.2 The AG commented that although the final scope for this appraisal did not consider sequencing of different technologies for the repair of cartilage defects, the place of ACI in the treatment pathway needs to be examined.

4 Clinical effectiveness evidence

ChondroCelect submission – clinical evidence

4.1 The submission supporting ChondroCelect provided evidence of clinical effectiveness from 4 sources: (1) the randomised controlled trial, TIG/ACT/01/2000; (2) a 'compassionate use' case series; (3) the registry-based cohort study, TGX001-2001; (4) the Belgian reimbursement scheme.

4.2 The TIG/ACT trial was a randomised controlled trial comparing first generation (ACI-P) ChondroCelect (n=57) with microfracture (n=61) in adults between 18 and 50 years with symptomatic cartilage defects of the femoral condyles (lesion size between 1 and 5 cm^2). Previous knee procedures had been performed on 37% of those in the ACI group and

21% of those in the microfracture group. At 60 months follow-up, ChondroCelect was associated with a greater overall KOOS score of 21.17 compared with 14.07 for microfracture, although this result was not statistically significant (p=0.068). The KOOS score comprised 5 subdomains: activities of daily living, pain, symptoms/stiffness, quality of life and function, sports and recreational activities. ACI was associated with a greater score compared with microfracture for each subdomain but the difference in each was not statistically significant. In addition, health-related quality of life outcomes using the SF-36 were numerically better for ChondroCelect compared with 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 affecting more than 20% of the index lesion, occurred in 13.7% of people in the ChondroCelect group and 16.4% of people in the microfracture group. Over the 5 years, more people in the ACI group experienced at least 1 related AE compared with the microfracture group (82% compared with 62%). The AEs were mostly mild to moderate in intensity. In a subgroup analysis, people with onset of symptoms of less than 3 years duration in the ChondroCelect group had a greater mean improvement in KOOS score than the microfracture group with a statistically significant difference of 10.69 (95% CI 1.30 to 20.07, p=0.026).

4.3 The ‘compassionate use’ case series was a non-comparative study of 370 people with symptomatic articular cartilage defects of the knee that were treated with second generation (ACI-C) ChondroCelect. There were no predefined entry criteria. The outcomes in this study were the Clinical Global Impression measures of improvement (CGI-I) and efficacy (CGI-E). The CGI-I outcomes ranged from very much worse to very much improved, with the results showing 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.

4.4 The registry cohort study (TGX001-2011) is an ongoing 'non-interventional' study initiated in Belgium and the Netherlands where ChondroCelect is funded. From the total 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 numbers at each follow-up period were not given. Six treatment failures (defined as the need for a re-intervention for more than 20% of the treated area) and 2 DVTs were among a total of 17 serious AEs observed.

4.5 The Belgian reimbursement scheme provided observational data regarding the number of ChondroCelect procedures in Belgium undertaken 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 increasing use of ChondroCelect, with 51 procedures 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 a further 2 patients failed between 12 and 24 months. Among the 51 people to reach 3 years follow-up no treatment failures were reported.

AG comments

4.6 The AG commented that the TIG/ACT trial was a good quality trial but results may now be better with second generation ACI-C. The AG stated that it regards first generation ACI-P (used in the TIG/ACT trial) as obsolete because it has no clinical advantages over second or third generation ACI and it requires more theatre time and has more subsequent costs (shaving of hypertrophy).

MACI submission – clinical evidence

4.7 The submission supporting MACI described clinical evidence primarily from the SUMMIT study (including the SUMMIT extension study), and Basad et al. (2010).

4.8 SUMMIT was an open-label, multicentre (16 European sites) randomised controlled trial comparing MACI with microfracture in 144 adults aged 18 to 55 years with symptomatic cartilage defects of the knee. Patients had a mean age of 33.8 years and a mean lesion size of 4.8 cm^2 (inclusion criteria for lesion sizes of 3 cm^2 or more). Previous knee surgery was observed for 90% of people in the MACI and almost 84% of people in the microfracture group. The co–primary efficacy endpoint was the change in the KOOS pain and function sub-scores from baseline at 2 years (n=137).There was a statistically 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 of 11.76, p=0.001; function: difference between ACI and microfracture of 11.41, p=0.001). There was a similar statistically significant improvement in the pain and function scores for a subgroup of people with a lesion size of less than 4cm^2. A statistically significantly greater improvement in secondary outcomes was also observed for patients treated with MACI compared with microfracture on the KOOS subscales of activities of daily living (difference between ACI and microfracture of 12.01, p<0.001), knee-related quality of life (difference between ACI and microfracture of 8.98, p=0.029), and other symptoms (for example, swelling, restricted range of motion [7 items]; difference between ACI and microfracture of 11.61, p=0.001).

4.9 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 designated commercial-in-confidence. The extension study is an open-label design comparing MACI (n=65) with microfracture

(n=63).[redacted]

4.10 Basad et al. compared 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 symptomatic chondral lesion of the femur or patella of a size between 4 and 10 cm^2. 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 ICRS scores, and were measured at 8 to 12 weeks, 22 to 26 weeks and 50 to 54 weeks after surgery. The definition of failure was not given. All patients underwent a post-surgery rehabilitation programme. 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. There was a statistically significant difference between baseline and 24 months post-operative scores for both MACI and microfracture for the Lysholm, Tegner, surgeon ICRS scores and patient ICRS questionnaire (all $p<0.0001$). MACI was associated with a statistically 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 ($p=0.02$) scores at 24 months.

4.11 The submission for MACI presented an indirect comparison of MACI and older generation ACI techniques. The indirect comparison included the 2-

year data from SUMMIT for (third generation) MACI (see section 4.8) and the TIG/ACT trial for first generation (ACI-P) ChondroCelect (see section 4.2), with microfracture as the common comparator. The indirect comparison showed no statistically significant difference between older generations of ACI and MACI in the likelihood of achieving a response to treatment. An indirect comparison was also carried out to compare MACI with mosaicplasty. This analysis used results from the Stanmore trial, published by Bentley et al. (2003), which was a randomised controlled trial comparing people with symptomatic chondral defects of the knee with either ACI (n=58) or mosaicplasty (n=42). Results of the Stanmore trial showed 'good' or 'excellent' results in 88% after first generation (ACI-P) or second generation (ACI-C) 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 had mosaicplasty had a statistically significantly lower likelihood of achieving a response compared with people who had first or second generation ACI (relative risk of 0.79, confidence interval of 0.63 to 0.98). Based on the finding that there was no statistically significant difference in treatment response rate between older first generation ACI-P and MACI (see section 4.11), the company argued that MACI would also be superior to mosaicplasty.

AG comments

4.12 The AG rated the quality of the Basad study using the modified Coleman methodology score as poor, although it stated that this was partly due to failure to report items. The AG commented that the Basad group has significant experience with ACI so their results may be better than might be seen in routine care. It also commented that the patients in the Basad study had fairly short duration of symptoms, which may improve outcomes after ACI. With regard to the SUMMIT study, the AG commented that the efficacy of ACI may have been underestimated relative to microfracture for 2 reasons. Firstly, because of the long duration of symptoms before ACI (people in the MACI group had knee symptoms for a mean of 5.8 years, and the microfracture group had knee symptoms for 3.7 years);

secondly, because of the high proportion (approximately 37%) that had previous knee surgery (not including diagnostic arthroscopy), which has been shown to reduce the efficacy of subsequent ACI procedures.

OsCell submission – clinical evidence

4.13 The OsCell submission reported clinical evidence for traditional ACI from 2 sources:

1. The ACTIVE trial: an ongoing multicentre randomised controlled trial of ACI (n=195; [redacted]). compared with standard treatment (n=195; could include microfracture [redacted], microfracture plus collagen membrane [redacted], mosaicplasty [redacted] 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 who were also considered suitable for ACI.
2. The REACT study: a cohort study of [redacted] patients with chondral or osteochondral defects treated with traditional ACI (not all in the knee – hips and ankles were also treated) in the RJAH Orthopaedic Hospital, Oswestry.

4.14 [redacted]

4.15 The submission included evidence from a study by McCarthy and Roberts (2013) which compared second generation ACI-C (n=55) with first generation ACI-P (n=33) from patients treated with the OsCell product (traditional ACI). The improvement in Lysholm score at latest follow-up (up to 13 years post-ACI) was not statistically significantly different between the 2 groups.

However, compared with ACI-P, the repair tissue formed from people treated with ACI-C demonstrated a significantly higher score for cellular morphology (ICRS II score), surface morphology from medial femoral condyle treated defects (ICRS II score) and a significantly higher proportion of hyaline cartilage formation (OsScore). These results were observed despite people having received ACI-C being significantly older at baseline than those having received ACI-P (mean age 38.7years compared with 34.2 years, p= 0.04), the mean size of the lesion treated with ACI-C being significantly larger than that treated with ACI-P (p=0.009), and despite the ACI-C treated patients having a significantly lower Lysholm score before surgery (p=0.04). The study concluded concluded from this that ACI-C is better than ACI-P as the former leads to repair of the defect with better quality tissue.

AG comments

4.16 The AG rated the quality of the ACTIVE study using the modified Coleman methodology score as good. It commented that not all of the listed serious adverse events from the ACTIVE trial looked serious, and noted that osteoarthritis was classed as a serious adverse event on the grounds that it represented treatment failure.

Assessment report – clinical effectiveness

4.17 The AG carried out a systematic review for clinical effectiveness data searching specifically for existing reviews that focussed on comparing the effectiveness of ACI (any generation) with microfracture. Twelve relevant systematic reviews were identified which included primary studies of first generation ACI-P compared with second generation ACI-C, ACI compared with MACI (third generation), open compared with arthroscopic ACI, ACI compared with mosaicplasty, and ACI compared with microfracture. The AG commented that ACI studies across the reviews were heterogeneous: follow-up was between 6.5 months and 7.5 years, mean age was between 26.4 and 40.4 years, between 47 and 80% were men, mean lesion size was between 1.9 and 6.4 cm^2 and duration of

symptoms before the intervention ranged between 1.5 and 10 years. The AG 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); the heterogeneities of patients recruited; variations in previous surgery, the ACI methods used, and the outcomes measured. Therefore the results of the identified reviews were considered to be mostly inconclusive on the choice between ACI and microfracture.

4.18 The AG noted the following observations from the reviews:

- There may be slightly longer delay with ACI than with other interventions to reach maximal functional improvement.
- ACI (all generations) may have a more durable long-term repair tissue compared with microfracture.
- Compared with second generation ACI-C, first generation ACI-P was associated with a higher rate of graft hypertrophy (over 20% compared with only 3%) and higher failure rates (7.7% compared with 1.5%).
- Outcomes were better for younger people, those who were more active, those with shorter symptom duration, and those who had not had a previous failed surgical intervention.
- Results were better for smaller lesions overall, but ACI produced better results compared with microfracture in larger lesions (and its effect was largely independent of lesion size).

4.19 The AG carried out a further systematic review of clinical trials that focussed on studies using second or third generation ACI between 2010 and 2014. The search excluded trials of first generation ACI on the basis that it has been replaced by second and third generation ACI. Two randomised controlled trials were identified in this review that were relevant to the decision problem, Saris et al. (2014; SUMMIT trial), and Basad et al. (2010) each comparing MACI with microfracture (the details

of these studies are summarised above in sections 4.9 and 4.10, respectively).

4.20 The assessment group commented that microfracture was significantly less expensive than ACI, and that it was effective in the short term in most patients. It suggested that on this basis one would expect microfracture to be used as a primary procedure, and ACI should be used if microfracture failed. However, it noted strong evidence from a study by Minas and colleagues that prior microfracture makes subsequent ACI less effective. The AG noted that this evidence implied that the benefits of ACI as a first procedure may be underestimated for studies in which ACI was used in people who had previous knee surgery. It also suggested that a case could be made for ACI to be used as the primary procedure.

4.21 The AG commented on the strengths and weaknesses of the clinical data, stating that there is now longer term follow-up than was available for previous appraisals, and data from several new trials: the ACTIVE trial has data up to 8 years follow-up (and will eventually have 10 years of follow-up on all patients); the TIG/ACT trial has 5 years of follow-up; the 2 trials of MACI compared with microfracture have currently 2 years of follow-up. The AG stated that there were limitations in the evidence because of the evolving nature of the technology, and because the longest term data come from versions of ACI which have been largely superseded. The AG stated that most, but not all, studies suggest that ACI is more effective than microfracture if used soon after the cartilage injury.

5 Comments from other consultees

5.1 A professional group, the British Association for Surgery of the Knee (BASK), made several points for consideration. It stated that when referring to size of the defect in terms of treatment options, it is important to consider the size of the defect in relation to size of the knee, and noted that a 2 cm diameter defect may be almost a half condyle width in a small

knee. With regard to comparators, it stated that osteotomy and total knee replacement are not comparators, and that only microfracture and mosaicplasty are surgical comparators. The professional group also commented on the evidence for the location of the lesion, and noted that the majority of randomised controlled trials are on femoral condyle defects as these are easier to recruit as a standard group. It stated that evidence is emerging in cohort studies when the location is the patella suggesting that patella lesions perform equally as well as condyle defects with ACI. It stated that mosaicplasty and microfracture perform poorly on the patella.

5.2 The patient group, Cell Therapy Catapult submitted a statement that argued for, although not specifically dictated by legislation, products supplied under the hospital exemption scheme to be excluded from NICE MTA when licensed products are available for the same indication. It stated that this is because hospital exemption products are not subject to the clinical development process including meeting rigorous regulatory requirements for scientifically proven quality, safety and efficacy that apply to licensed products

6 Cost effectiveness evidence

ChondroCelect submission – cost effectiveness

6.1 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 was 75 years. The model structure allowed both temporary and permanent successes of ACI. If either microfracture or ACI failed, the patient had debridement and then either went on to have a second repair (second repair would be microfracture only), or the patient was offered pain relief. If the second repair failed the patient had debridement and pain relief only. The model used clinical effectiveness data on the time to treatment failure from the TIG/ACT trial. Utility scores were obtained from a paper by Gerlier et al. (2010) in which KOOS scores and responses to the SF-36 questionnaires collected up to 60 months

post-surgery in the TIG/ACT trial were analysed and used to derive utilities (see table 7 of appendix B for the utility scores associated with each health state).

6.2 The model used NHS reference costs and a cost for ChondroCelect of £16,000 (see table 8 of appendix B for the costs used the model). The cost of procedures included the costs of surgery, inpatient stays and physiotherapy follow-up. The cost of arthroscopy and cell harvest (procedure 1) was £722.45, and the cost of arthrotomy conducted in an outpatient setting (procedure 2) was £109.65. The total cost of ACI was £22,586, and the total cost of microfracture was £13,547. 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. Microfracture was the only comparator in the model. The key assumptions of the model were that fewer patients who had ACI needed second repairs and that patients that had ACI had a longer duration of success (which postponed the need for a knee replacement). Total QALYs gained for ACI compared with microfracture were 1.29. The corresponding ICER for ACI compared with microfracture was £7,077 per QALY gained. The main driver of cost effectiveness was the time to failure of the first repair.

AG comments

6.3 The AG stated that the economic model in the ChondroCelect submission was logical. It stated that the cost for implantation of the cells was an under-estimate because the procedure would be done as a day-case not an outpatient visit. It commented that the utility values were plausible, that it was a reasonable assumption for microfracture to be the only relevant comparator for ACI and that overall the model assumptions and results looked plausible.

MACI submission – cost effectiveness

6.4 The submission for MACI did not present a cost effectiveness analysis but did provide a budget impact/costing forecast for England and Wales

based on the assumption that there would be 500 ACI procedures, half of which would be with MACI. It explored 2 scenarios, one with MACI or ACI as the first procedure, and the other with microfracture as the first procedure, and then calculated the difference in costs between these 2 scenarios to estimate the budgetary impact. Based on data for failure rates from the SUMMIT trial, it estimated that there would be cost-savings from using MACI/ACI of £5.9 million in year 1 to £8.3 million in year 5. These savings were due to the lower reoperation rate after MACI/ACI.

AG comments

6.5 The AG commented that the budget impact cost calculations provided in the MACI submission seemed reasonable and plausible.

OsCell submission – cost effectiveness

6.6 The OsCell submission provided a prospective cost-effectiveness analysis for the ACTIVE trial but did not present an economic model. The analysis used quality of life (EQ-5D) data based on up to 8 years of follow-up. The costs for ACI were stated according to the National Tariff Payment System (2014/2015) as reimbursed to the RJAH hospital and included operations, hospital stays, the cells and any further implants. It assumed a cost for the first ACI procedure of £2,398 and a cost for the second stage procedure of £6876 (including the cost for cells based on production by OsCell of £4125). The total cost of ACI was therefore £9274, or £9565 when an additional 'market forces factor' was taken into account. The submission stated that the incremental cost of ACI over microfracture was [redacted].

AG comments

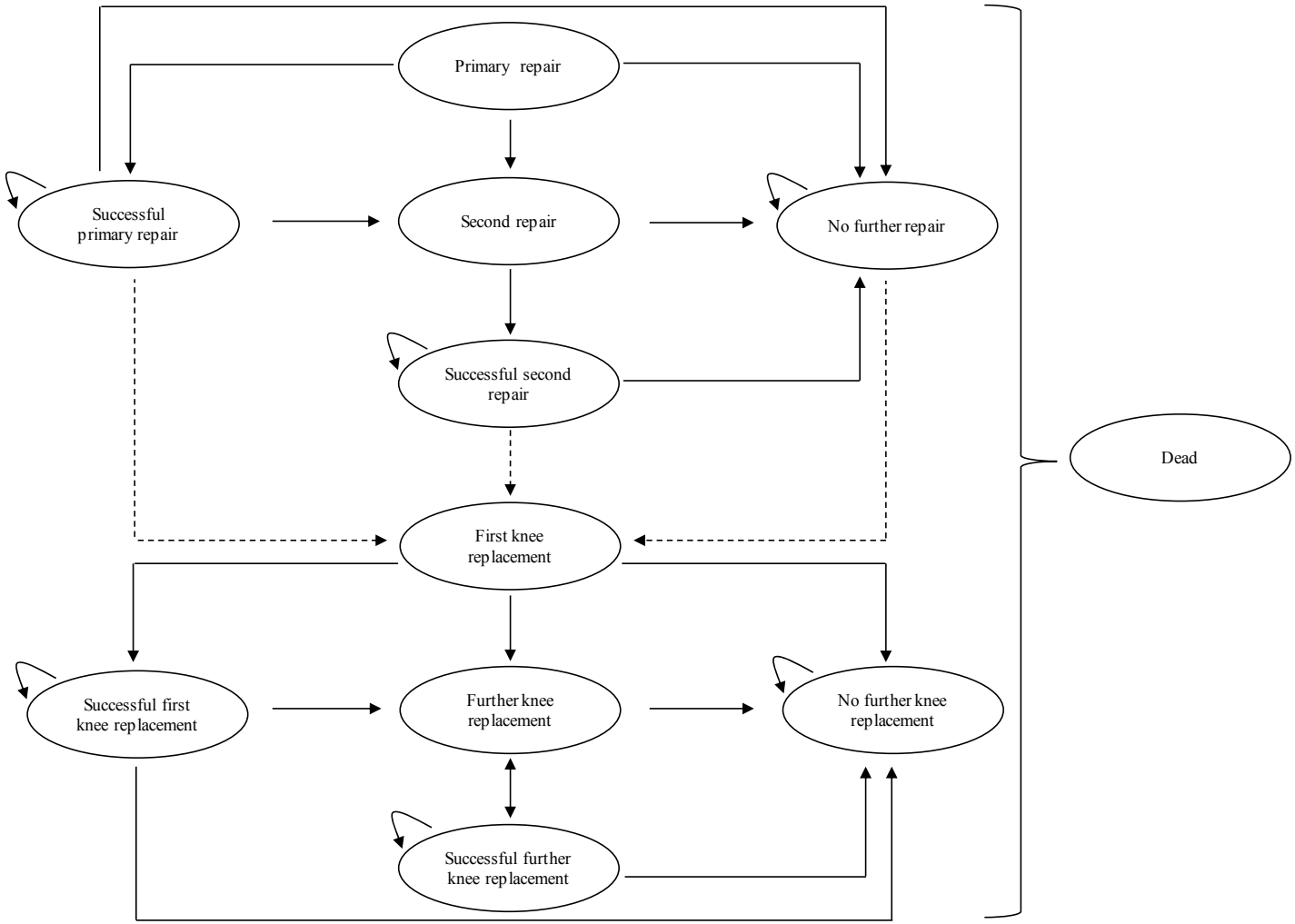
6.7 The AG commented that it was not clear how the reported EQ-5D results were converted to QALYs. It also noted that the [redacted].

Assessment report – cost effectiveness

6.8 The AG 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.

6.9 The AG constructed a Markov model of the cost effectiveness of ACI as a class compared with microfracture (model structure is shown in Figure 1; see table 6 of appendix B for details of the main model inputs and a comparison with those of the ChondroCelect model). The model uses a lifetime horizon (patients can live to 100 years) and a cycle length for the model set at 1 year and transitions between each health state occurring at the end of each cycle. A hypothetical cohort of 1000 people with symptomatic articular cartilage defects of the knee with a starting age of 33 years is followed (many people with cartilage injury are young and involved in sports which is where most of the injuries occur) from their first repair with either an ACI or microfracture. The analysis was conducted from the perspective of the NHS and personal social services (PSS). An annual discount rate of 3.5% was applied to both costs and outcomes. The main comparison was between ACI and microfracture. The base-case analysis used data mainly from the TIG/ACT trial of ChondroCelect and the SUMMIT trial of MACI, both of which compared ACI with microfracture, and data for knee replacement was taken from published literature. The dashed line in the model indicates that at 55 years, the person can choose to have a knee replacement (total or partial).

Figure 1. Markov model structure for patients with articular cartilage defects of the knee joint



6.10 The analysis considered a number of outcomes after the first procedure, including permanent success, temporary success or failure. Permanent success meant the person could stay in the successful primary repair health state until they die. Using response rates taken the SUMMIT study for MACI it was assumed that most patients (87.5% who had ACI as a primary procedure, and 68.1% who had microfracture as primary procedure) did not need a second repair. For temporary success (in the remaining patients), the analysis considered the need for subsequent further repairs or later total or partial knee replacement(s). The AG presented 2 scenarios following a first repair with either ACI or microfracture:

- scenario 1: all second repairs were ACI
- scenario 2: all second repairs were microfracture.

With repair failure, a person could have another repair, or could decide against another repair and treat symptoms with pain medication. The person would probably develop osteoarthritis, and may have 1 or more knee replacements in later life. It was assumed that people over the age of 55 could not have an ACI and could only have a knee replacement or symptomatic care. Adverse events were not included as there were no important differences between ACI and microfracture. For the base-case analysis, data was mainly for the knee repairs from the TIG/ACT trial of ChondroCelect and the SUMMIT trial of MACI, both of which compared ACI with microfracture (see table 1). For knee replacement, data was used from published literature.

Table 1. Sources of the progression rates used to calculate transition probabilities between different health states

Health state	Progression rates used to calculate transition probabilities	Study details for source
Patients receiving an ACI procedure (all second repairs ACI)		
Primary repair	Based on 3-year progression rates for people who progressed from primary repair to: • Successful primary repair: rate of 83.0% • Second repair: rate of 3.9% • No further repair: rate of 13.1%	Saris et al (2009) TIG/ACT study – 3 year results ACI-P with ChondroCelect vs MF
Successful primary	Based on 2-year progression rates for people who progressed from a successful primary repair to: • Remain in successful primary repair: 87.5% • 12.5% move to no further repair state and of these 12.5%, 10% will move from the successful primary to the second repair health state.	Saris et al (2014) SUMMIT study – 2 year results MACI vs MF
Second repair	Assumed to be the same as primary repair rates except there are no further repairs (83% success vs 17% failure over 3 years)	Saris et al (2009) TIG/ACT study – 3 year results ACI-P with ChondroCelect vs MF
Successful second	Assumed to be the same as a successful primary: 87.5% remain in successful second state, vs 12.5% who move to the no further repair health state.	Saris et al (2014) SUMMIT study – 2 year results MACI vs MF
Patients receiving an MF procedure (all second repairs MF)		
Primary repair	Based on 3-year progression rates for people who progressed from primary repair to: • Successful primary repair: rate of 62.0% • Second repair: rate of 11.5% • No further repair: rate of 26.5%	Saris et al (2009) TIG/ACT study – 3 year results ACI-P with ChondroCelect vs MF

Successful primary	Based on 2-year progression rates for people who progressed from a successful primary repair to: • Remain in successful primary repair: 68.1% • 31.9% move to the no further repair health state and of these 31.9% patients, 10% will move from successful primary to second repair	Saris et al (2014) SUMMIT study – 2 year results MACI vs MF
Second repair	Assumed to be the same as primary repair rates except there are no further repairs (62% success vs 38% failure over 3 years)	Saris et al (2009) TIG/ACT study – 3 year results ACI-P with ChondroCelect vs MF
Successful second	Assumed to be the same as a successful primary: 68.1% remain in successful second state, vs 31.9% who move to the no further repair health state.	Saris et al (2014) SUMMIT study – 2 year results MACI vs MF
Patients receiving an ACI procedure (all second repairs MF)		
Second repair	People who had a second repair can have a successful second repair (rate of 83.6% at 5 years) or do not receive a further repair (rate of 16.4% at 5 years).	Vanlauwe et al (2011) TIG/ACT study – 5 year results ACI-P with ChondroCelect vs MF
Successful second	68.1% remain in successful second state, vs 31.9% who move to the no further repair health state.	Saris et al (2014) SUMMIT study – 2 year results MACI vs MF
Patients receiving an MF procedure (all second repairs ACI)		
Second repair	People who had a second repair can have a successful second repair (rate of 69.1% at 10 years) or do not receive a further repair (rate of 30.9% at 10 years).	Biant et al (2014) – case series following ACI-C (n=85) and ACI-P (n=19)
Successful second	68.1% remain in successful second state, vs 31.9% who move to the no further repair health state.	Saris et al (2014) SUMMIT study – 2 year results MACI vs MF

6.11 The model used utility values for knee repairs from a study by Gerlier et al. who compared ACI with MF using data from the TIG/ACT ChondroCelect trial. The Gerlier study used a short-term model with a time horizon of 5 years to take into account knee pain and mobility after the initial intervention (quality of life information was obtained from a 5 year randomised controlled trial using the SF-36 questionnaire) and also a long-term model with a time horizon of 40 years to take into account the development of osteoarthritis after 15 years and the need for a total knee replacement after 20 years. The AG used 2 other studies to supplement utility values for knee replacement and knee arthroscopy. Utilities are presented in table 2. Further information on the source of utility values is found of pages 102 to 105 of the Assessment Report.

Table 2 Base-case mean utility values used in the AG's economic model

	First repair ACI		First repair MF		Source
Repairs					
Before primary repair	0.654				Gerlier et al (2010)
Successful primary					
1st year	0.760		0.760		Gerlier et al (2010)
2nd year	0.817		0.817		Gerlier et al (2010)
3rd year	0.817		0.817		Gerlier et al (2010)
4th year	0.817		0.817		Gerlier et al (2010)
5 years +	0.817		0.654		Gerlier et al (2010)
Before second repair	0.654				Gerlier et al (2010)
Choose not to have a second repair	0.691*				Gerlier et al (2010)
Second repair	**ACI**	**MF**	**ACI**	**MF**	
Successful second					
1st year	0.760	0.760	0.760	0.760	Gerlier et al (2010)
2nd year	0.817	0.817	0.817	0.817	Gerlier et al (2010)
3rd year	0.817	0.817	0.817	0.817	Gerlier et al (2010)
4th year	0.817	0.817	0.789	0.817	Gerlier et al (2010)
5 years +	0.817	0.654	0.789	0.654	Gerlier et al (2010)
No further repair	0.691				Gerlier et al (2010)
Replacements					
Before first KR (TKR)	0.615				Dong & Buxton (2006) and Jansson & Granath (2011)
Before first KR (PKR)	0.615				Dong & Buxton (2006) and Jansson & Granath (2011)
Successful first KR - TKR	0.780				Dong & Buxton (2006)
Successful first KR - PKR	0.780				Dong & Buxton (2006)
Before further TKR	0.557				Gerlier et al (2010)
Successful further TKR	0.780				Dong & Buxton (2006)
No further TKR	0.691				Gerlier et al (2010)

6.12 Costs for the different procedures (ACI, microfracture, partial or total knee replacement) and for outpatient visits and rehabilitation are shown in table 3. The model used national reference costs where possible (NHS references costs, 2013) supplemented by the previous HTA report on cartilage defects in knee joints (Clar et al, 2005). All unit costs were presented in pounds sterling (£) in 2012/13 prices.

Table 3. 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)
	Total cost	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)

* Cost inflated to 2012/13 prices using the HCHS index [Curtis, 2013]

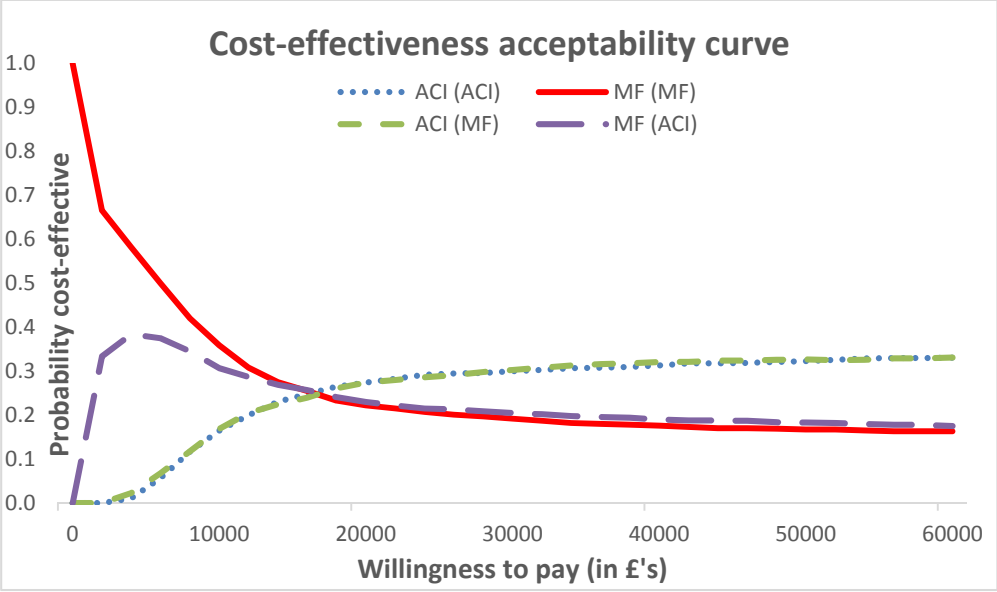
The cost of the ACI (ChondroCelect and MACI) included the costs associated with cell development, including the ACI kit, staff time and transporting the cells to and from the laboratory. It assumed the 2 procedures in an ACI (removal of the cells, and implantation) could be performed as day cases. The cost of the microfracture procedure included an inpatient stay because, unlike after ACI, the patients can have considerable pain after microfracture because of the drilling into bone. Based on consultation with clinical experts, the model also included the costs outpatient visits and rehabilitation visits in the first year (see table 4).

Table 4. Base-case resource use for economic model

Components (over a year)	Procedure			Source
	ACI	MF	TKR	
Inpatient days	0	1	4.5	Expert clinical opinion
Outpatient visits	6	3	2	Expert clinical opinion
Rehabilitation visits	3	3	0	Expert clinical opinion

6.13 The AG used the term ACI as a generic term to cover all relevant forms of ACI. The base-case discounted ICER for ACI compared with microfracture ranged from over £14,395 per QALY gained (if the second repair was ACI in both arms) to £15,598 per QALY gained (if the second repair was microfracture in both arms). Figure 2 presents the cost-effectiveness acceptability curve for the base-case results for all sequences. The graph shows that at a willingness to pay of £18,000 or more for a QALY, ACI as a first procedure (followed by a potential second repair of ACI or microfracture) is likely to be more cost-effective than if microfracture is used as a first procedure (followed by potential second repairs of ACI or microfracture).

Figure 2. Cost-effectiveness acceptability curve. The choice of a potential second repair is represented in parentheses.



6.14 The first sensitivity analysis was performed because the AG stated that it is known that there are confidential discounts provided to the NHS by manufacturers. To represent this, the AG applied between 25% and 75% discounts to the acquisition cost of the cells which led to a reduction in the ICER (if the second repair was ACI in both arms) from approximately £14,400 per QALY gained in the base case to £10,523 (25% discount), £6651 (50% discount) and £2779 (75% discount; approximately the same acquisition cost of traditional ACI) per QALY gained. If the second repair was microfracture in both arms the base case ICER reduced from approximately £15,600 per QALY gained in the base case to £11,404 (25% discount), £7210 (50% discount) and £3016 (75% discount). The AG carried out further analyses using utility data from the ACTIVE trial (as presented in the OsCell submission), using costs of both commercially produced cells and OsCell cells.

[redacted]

6.15 The key drivers in the base case were the cost of cells for ACI and the relative durations of benefit derived from ACI and microfracture. Although there was some variation among studies, after the first few years after treatment, ACI provided a greater gain in QALYs and led to greater cost savings to the NHS because fewer people needed a second repair or a knee replacement, and also the need for a first knee replacement was postponed which reduced the need for second knee replacement.

6.16 The AG commented that the limitations in the economic analyses included uncertainties with long-term progression rates and quality of life data. It stated that longer-term data from the ACTIVE trial will provide useful information in the future.

7 Equality issues

7.1 Both ChondroCelect and MACI products contain animal derived products which may be an issue for people with particular religious and cultural beliefs. The ChondroCelect submission states that the optimal patient group for treatment with ChondroCelect is people aged 18 to 50 years (the population of TIG/ACT study) but it would be important not to discriminate potentially healthy patients based on age alone

8 Innovation

8.1 ACI products are considered as "regenerative medicines" which are inherently innovative. The ChondroCelect submission stated that ChondroCelect has regulatory approval for its controlled and consistent manufacturing process, based on optimised parameters that include enzymatic release, cell culture media, seeding density, time, harvesting procedures and shipping conditions. The submission details the use of characterised chondrocyte implantation (CCI) which it stated results in highly chondrogenic cells by minimising chondrocyte dedifferentiation and thereby preserving the behaviour and appearance of articular hyaline cartilage cells (rather than fibrocartilage). The ChondroCelect submission also noted other advantages of CCI compared with microfracture and mosaicplasty, which are detailed in table 5:

Table 5. Summary of advantages of CCI compared with microfracture and mosaicplasty (adapted from page 15 of the ChondroCelect submission

Cell-based therapy vs	Advantage of CCI
Microfracture	CCI with ChondroCelect produces cartilage more closely resembling the original hyaline cartilage rather than fibrocartilage.[31]
Microfracture	The ChondroCelect implant does not form a clot and therefore is not associated with clot retraction.
Microfracture Mosaicplasty	CCI results in less damage to the anatomy of the knee in the area of the cartilage damage, minimising further damage to the surface of the cartilage and reducing the chances of inducing or accelerating the development of OA. • In the case of microfracture, the tidemark and subchondral bone plate are breached and may lead to bone-forming cells accessing the area of the defect; this is thought to contribute to the deterioration of

	symptoms and the development of OA. • In the case of mosaicplasty, the anatomy is altered at both the donor site (in autografting) and the implantation site (in both autografting and allografting) making it difficult to ensure congruence between the opposing surfaces.
Mosaicplasty	The ChondroCelect implant is fluid which allows it to adopt a shape that fits the surface required by the position of the lesion and the contours of the opposing surface.
Mosaicplasty	CCI does not involve creating injury in the donor site.
CCI, characterised chondrocyte implantation; OA, osteoarthritis.	

8.2 The MACI submission stated that MACI is a third generation ACI which represents a marked improvement over the first 2 generations. It stated that compared with the OsCell product and ChondroCelect, MACI is easier to use, as it can be easily cut to size and shape by the surgeon. It also cited evidence by Barlett that MACI implantations are quicker to implant meaning they require less theatre time.

8.3 The OsCell submission stated that if changes were to be made to make ACI more easily and widely available to more patients, it could certainly make a 'step-change' in the treatment of the degenerate joint. It also stated that there are additional health-related quality of life benefits as a result of ACI which the EQ-5D would not capture, including the likely alleviation or delay of a joint replacement, which is not only costly, but also restricts the activity levels and well-being of the patients.

9 Authors

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Appendix A: Supporting evidence

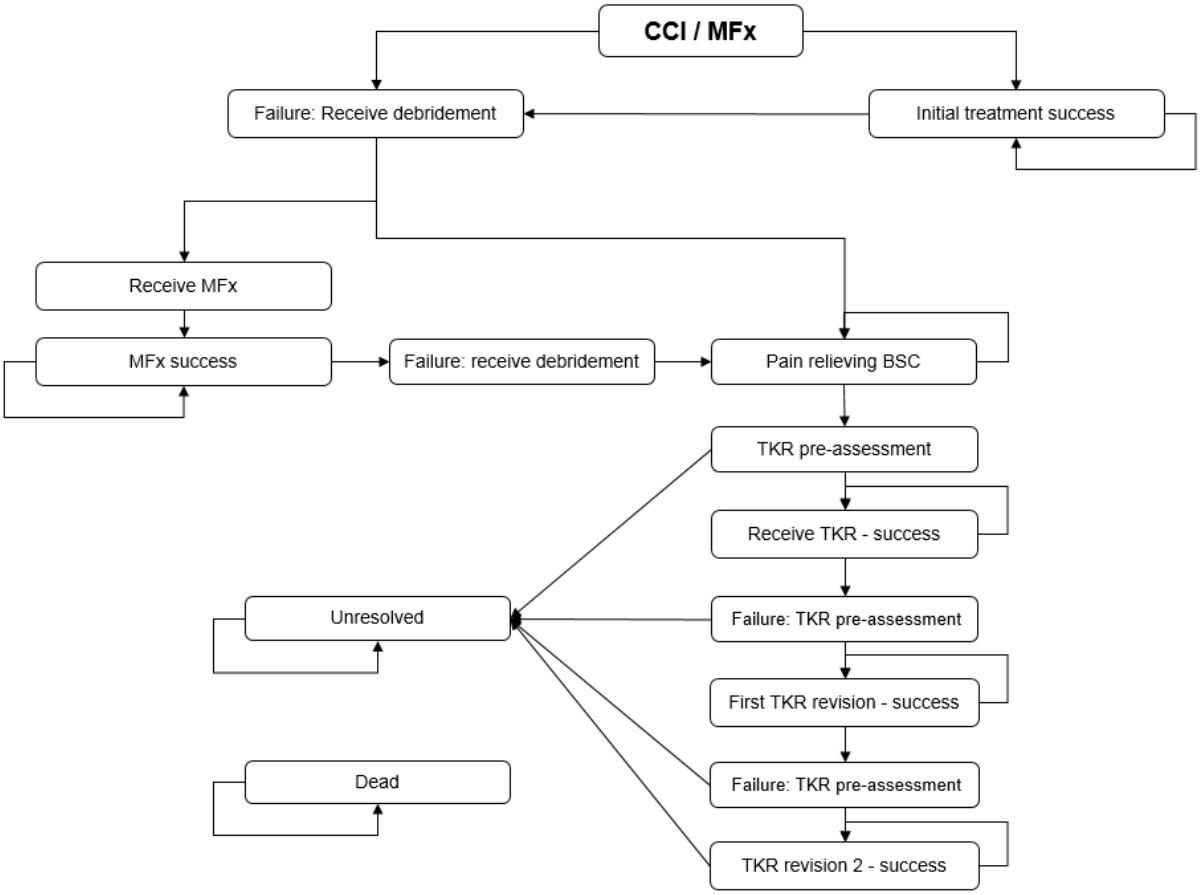
Related NICE guidance

Published

- 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)
- 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)

Appendix B: Supporting evidence

Figure 3. Model structure presented in the ChondroCelect submission



BSC, Best supportive care; CCI, characterised chrondrocyte implant; MFx, microfracture; TKR, total knee replacement

Table 6 Comparison of main model inputs between the ChondroCelect model and the AG model

	ChondroCelect Model	AG Model
Model structure	Markov model structure that allows temporary and permanent success (see figure 3, page 39)	Markov model structure that also allows temporary and permanent success (see figure 1, page 27)
Comparators	Microfracture only	Microfracture only
Perspective	NHS and Personal Social Services	NHS and Personal Social Services
Cycle length	1 month	1 year
Discounting	3.5% per annum	3.5% per annum
Mean age of patients receiving a procedure	33.9 years	33 years
Time horizon	75 years	Lifetime horizon (patients can live to 100 years)
Separated by gender	Yes (35.6% female)	No
Allows temporary and permanent success	Yes	Yes
Assumptions around second repair	Microfracture only: it was assumed, based on clinical advice, that when ACI fails, 90% of patients will receive MF and when MF fails only 5% of patients receive another MF Assumed based on clinical advice that a second MF following a first MF would be half as effective	Microfracture or ACI: 4 scenarios: ACI(ACI), ACI(MF), MF(MF), MF(ACI)
Assumptions around TKRs	Maximum number of 3 TKRs TKRs suitable for 95% of cohort	Maximum number of 2 knee replacements First knee replacement can be either partial total Knee replacements suitable for people over 55 years of age
Main clinical data inputs for ACI	Used TTF from 5 year results of and subsequent compassionate use programme Used data for ACI-P with ChondroCelect vs MF (Vanlauwe et al 2011). Used TTF data as a proxy of treatment efficacy: hence, it assumed everyone who did not receive a subsequent therapy was a 'success'.	See table 1 for details. Used TIG/ACT study (3 year results rather than the 5 year results) Key difference between AG and ChondroCelect models is that the AG model allows for failure based on TTF data but also uses the longer term response data: hence, it assumes non-responders have also 'failed'.
Costs	See table 8	See table 3
Utilities for knee repairs	See table 7: based on TIG/ACT data by Gerlier et al.	See table 2: based on TIG/ACT data by Gerlier et al.

<table>
<tr><td></td><td></td><td>Assumes that the utility for patients after MF for Year 5 and beyond is lower than previous years (ACTIVE data)

Sensitivity analysis used data from the ACTIVE study</td></tr>
<tr><td>Adverse events</td><td>Not included</td><td>Not included</td></tr>
<tr><td>Results</td><td>Incremental costs for ACI vs MF: £8,890 and £9,129 (corrected by AG)

Incremental QALYs for ACI vs MF: 1.29

ICER for ACI compared with MF was £7,077 per QALY (corrected by AG)</td><td><table>
<tr><th>Procedure</th><th>Incremental costs £</th><th>Incremental QALYs</th><th>ICER £ (cost per QALY gained)</th></tr>
<tr><td>MF (ACI)</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>ACI (ACI)</td><td>14,524</td><td>1.6273</td><td>8,925</td></tr>
<tr><td>MF (MF)</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>ACI (MF)</td><td>14,921</td><td>1.5245</td><td>9,788</td></tr>
<tr><td>MF (ACI)</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>ACI (ACI)</td><td>14,314</td><td>0.9944</td><td>14,395</td></tr>
<tr><td>MF (MF)</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>ACI (MF)</td><td>14,877</td><td>0.9537</td><td>15,598</td></tr>
</table></td></tr>
<tr><td>Main cost drivers</td><td>The cost of the cells and the fact that fewer people needed further repair or TKR with ACI compared with microfracture.</td><td>The cost of the cells, but over the lifetime horizon, there are QALYs gained from using ACI, and there are cost savings to the NHS later due to fewer people needing a second repair, fewer people in need of a TKR, and fewer people moving to the no further repair/replacement health states.</td></tr>
</table>

Table 7 Utility scores associated with the main health states of the ChondroCelect economic model (adapted from page 49 of ChondroCelect submission)

Health state	Value	Source/method	Applicable health states
Initial score (pre-surgery)	0.6540	Predicted baseline utility score (linear functional regression: KOOS/utility)	During initial CCI or MFx procedure
Clinical success after surgery	0.8170	Average utility of KOOS responders[a]	Successful CCI or MFx (including subsequent MFx)
No clinical success after surgery	0.6910	Average utility score of KOOS non-responders[a]	Receiving BSC
Undergoing a TKR	0.5177	Batty & Birrell, 2011	During TKR or TKR revision procedure
Following successful TKR and/or revision	0.6830	Utility with osteoarthritis plus the difference between the utility of successful surgery and pre-surgery	Following successful TKR and/or revision
Unresolved (unsuitable for TKR or failed TKR/revision)	0.5570	Utility with osteoarthritis plus the difference between no clinical success after surgery and pre-surgery	Unresolved cases

Key: BSC, best supportive care; CCI, characterised chondrocyte implantation; EQ-5D, EuroQoL five dimensions; KOOS, Knee injury and Osteoarthritis Outcome Score; MFx, microfracture; SF-6D, Short form six dimensions; TKR, total knee replacement.

Note: [a] Utility estimated by KOOS response used as a proxy for patients having successfully resolved defects.

Table 8 Base-case mean costs used in ChondroCelect economic model (adapted from page 46 of ChondroCelect submission)

Treatment	Details	Unit cost	Source
ChondroCelect	Product including two-way courier and development of cell culture	£16,000	UK price of ChondroCelect
	Procedure (1 of 2) – arthroscopy and cell harvest	£722.45	Clar *et al*
	Procedure (2 of 2) – arthrotomy, outpatient setting	£109.65	NHS (Trauma & orthopaedic)
MFx – base case analysis cost	Procedure, inpatient setting, rehabilitation	£2,817,79	Clar *et al* (Aberdeen Royal Infirmary)
MFx – scenario analysis cost	Procedure, day case, rehabilitation	£964.87	Clar *et al* (Southampton General Hospital)
Debridement and arthroscopy	Procedure	£722.45	Clar *et al*
TKR	Procedure, rehabilitation	£6,500.85	Clar *et al*
TKR revision	Procedure, rehabilitation	£12,093.24	Clar *et al*

Key: HCHS, Hospital & Community Health Services; MFx, microfracture; TKR, total knee replacement.
Note: Costs reported by Clar *et al* were uplifted using the HCHS index inflation indices: 2005-06 (240.9) vs. 2012-13 (289.1).