MULTIPLE TECHNOLOGY APPRAISAL (MTA)

AUTOLOGOUS CHONDROCYTE IMPLANTATION FOR REPAIRING SYMPTOMATIC ARTICULAR CARTILAGE DEFECTS OF THE KNEE

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Report by OsCell

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Manufacturer of MHRA Licensed Products: Autologous Chondrocytes

Autologous bone marrow-derived stromal cells

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1. INTRODUCTION

OsCell's John Charnley Laboratory manufactures culture-expanded Autologous Chondrocytes as an Advanced Therapy Medicinal Product (ATMP), in addition to autologous bone marrow-derived MSCs. The technology currently under appraisal is the implantation of autologous chondrocytes into patients with symptomatic chondral and osteochondral defects in knee joints, known as Autologous Chondrocyte Implantation (ACI). The OsCell product does not have a marketing authorisation but is manufactured under an MHRA Manufacturing and Importation Authorisation for Investigational Medicinal Products (MIA[IMP]) licence No. 21276. Additionally we have applied for a Hospital Exemption Licence. Two other ACI products have been licensed by the EMA in Europe in the form of MACI®by Sanofi (the marketing authorisation having recently been transferred to Aastrom Biosciences DK ApS August 26th 2014, EMEA/H/C/2522/T/3) and ChondroCelect by TiGenix. ACI with periosteum has FDA approval in the USA.

The Robert Jones and Agnes Hunt Orthopaedic Hospital (RJAH), Oswestry, has been treating patients with OsCell-manufactured autologous chondrocytes since 1997. In 1999, OsCell moved into the purpose-built John Charnley Laboratory manufacturing suite. Thirty to forty patients are currently treated with ACI each year at RJAH.

2. CONTEXT OF THIS REPORT

Oscell's John Charnley Laboratory manufactures culture-expanded autologous cells in an NHS cell manufacturing facility based in a specialist orthopaedic hospital, the Robert Jones and Agnes Hunt Orthopaedic Hospital NHS Foundation Trust (RJAH). Oscell, which employs 1 fulltime and 2 part-time employees, has resulted from co-operation between RJAH NHS Trust, Keele University and a local charity, the Orthopaedic Institute Ltd (Reg no. 1044906).

Five sources of evidence are reported in this submission:

Appendix 1: REACT. A cohort study of 162 patients treated with ACI to the knee at RJAH between 1996 and 2010 using OsCell manufactured chondrocytes.

Appendix 2: ACTIVE. The multicentre prospective randomised controlled ACTIVE trial (Autologous Chondrocyte Transplantation/Implantation Versus Existing treatments), sponsored by Keele University, hosted by RJAH and funded by the Medical Research Council (MRC). 390 patients were randomised to receive either autologous chondrocytes or control treatment (microfracture, microfracture plus collagen or mosaicplasty). Cells used were either OsCell manufactured

chondrocytes or chondrocytes from commercial manufacturers. Follow-up for this trial is still underway.

Appendix* 3: *Studies of quality of repair (by MRI, histology and biochemical analyses)

Appendix 4: A comparison of the different forms of ACI. A literature review focussed on different studies of ACI.

3. BACKGROUND

Chondral defects may occur after trauma, or spontaneously. Whatever the cause, the defect is unlikely to heal satisfactorily and inflammation develops in the adjacent synovium. The symptomatic defect tends to enlarge with time. Some patients can control symptoms by limiting activity levels and may manage for a decade or two without significant progression. In most cases, however, the defect progresses and other defects may also develop, the joint space narrows, osteophytes form and stiffness and pain increase. Some simple surgery such as debridement may help and encourage the healing process (Hubbard et al., 1996). The Hubbard study is of note as it included a control group where arthroscopy alone was used. The control group did not have spontaneous improvement in symptoms at 5 years, evidence of the need for a surgical treatment. Many different types of treatment have been developed over the last 20 years, in particular microfracture, mosaicplasty and autologous chondrocyte implantation (ACI). An osteotomy within the joint may be appropriate if there is underlying malalignment, or joint replacement may be indicated if the disease has progressed too far.

Osteochondral defects involve loss of both bone and cartilage in a joint. A particular condition of osteochondritis dissecans affects the knee with a prevalence of approximately 1 in 5000. This may heal in the teenage patient, or may require surgery to fix a loose osteochondral fragment. If osteochondral defects persist into patients' early 20's then they tend not to heal spontaneously but gradually increase their symptoms. Treatment options include bone grafting, ACI or osteochondral allografts. In due course knee replacement may be indicated.

As described in the NICE document 'Appendix B - Final Scope', ACI has been introduced as one of the treatment options to re-establish the articular surface in a joint with symptomatic chondral defects. The interest in successful treatment of such defects is due to the belief that if left untreated, they are likely to lead to the development of osteoarthritis in that joint with the consequent likely eventual need for arthroplasty. Unfortunately if joint replacement is performed in the younger

patient then there is a significant risk of early revision with 14% of uni-compartmental knee replacements in the knee failing by 5 years (Australian Joint Registry: https://aoanjrr.dmac.adelaide.edu.au/). Subsequent surgery is more costly than primary surgery and carries a significant risk of infection, further failure and a lifetime risk of above-knee amputation. This risk of expensive and repeated surgery occurs in 1 in 270 patients who have a knee replacement below the age of 50 years. An above-knee amputation leads to significant loss of mobility, and some patients have severe persisting pain. Knee replacement itself leads to significant pain and stiffness in 10% of patients, such that many patients do not have good function. It is for this reason that both patient and surgeon seek alternatives to treat early arthritis in the knee with the aim of at least delaying joint replacement and avoiding a revision surgery in later life. Results from other centres demonstrate that ACI is appropriate for treating joints with early OA in the younger patient (Minas et al 2010). They reported that 92% of patients (mean age 38 years at time of treatment) were functioning well at 5 years postoperatively and were able to delay the need for joint replacement. They conclude that given the limited number of treatment options for young osteoarthritic patients, autologous chondrocyte implantation may offer improved quality of life to this subset of patients. Minas et al (2009) have also reported that treatment of primary lesions is beneficial in comparison to those in which a previous chondral repair technique, such as microfracture, has been performed. Defects that had treatment involving breaching the subchondral plate prior to ACI, resulted in 3 times as many failures of ACI than those treated first with ACI.

Only chondrocytes can form cartilage. We believe that the regeneration of cartilage with a cell therapy is the most appropriate solution to treat chondral defects, as cartilage is the evolved solution to providing good joint function.

3.1 Mechanism of action

Autologous chondrocyte implantation (ACI) was first described in 1994 by Brittberg *et al*. ACI involves obtaining a cartilage biopsy from a healthy area of articular cartilage, chondrocytes are then isolated and expanded in monolayer culture, and implanted within the cartilage defect, under a periosteal flap or a synthetic collagen membrane (Brittberg et al., 1994). It is theorised that the implanted chondrocytes are the main producers of the new tissue that is formed within the defect (Lutianov et al., 2011), and studies of tracked chondrocytes do indeed confirm that they form cartilage in the defect (Dell'Accio et al, 2003). Chondrocytes cultured by Oscell and inserted into chondral defects in patients are known to synthesise a mixture of hyaline and fibrocartilage matrices comprising collagen types I, II and X, and proteoglycans (Roberts et al., 2003). In this way the applied

chondrocytes fill the defect and restore a substantial thickness of new repair cartilage which protects the underlying bone from fluid incursion and provides a low friction surface for smooth articular joint motion. In addition, these chondrocytes attach to the freshly cut surfaces of cartilage at the edge of treated defects to provide lateral integration of repair tissues (Roberts et al., 2003).

Two randomised controlled clinical trials have demonstrated superiority of chondrocyte cell therapy over microfracture, the SUMMIT trial of MACI (Saris et al 2014) and the TiGenix trial of ACI with Chondrocelect (Saris et al 2008). Superiority for one treatment compared to another is most often described in terms of the structure of the repair cartilage as resembling a hyaline versus fibrocartilage composition and organisation. In these terms, early comparisons have shown that ACI is also superior to mosaicplasty (Bentley et al., 2003) and, in terms of functional outcome, the ACI procedure has shown improved functional outcome compared to mosaicplasty in a 10-year follow-up study of 100 patients with large joint lesions (Bentley et al., 2012).

3.2 The Comparators

Mosaicplasty, microfracture and ACI all became available in the same period. Mosaicplasty is now rarely used as it is technically demanding. Microfracture carries concerns about bone ingrowth into a defect, or other unknown effects that limit the options for subsequent treatment following failure (Minas 2009). ACI has become difficult due to the recommendation from NICE to perform it only in the context of long term studies and the licencing requirement from the Human Tissue Authority for taking a cartilage biopsy, both of which are difficult outside specialist centres.

Micro-drilling has been introduced, chondroplasty is being tried and the application of different matrices (for example AMIC or Hyalofast) are being used.

Osteochondral transplantation is increasing in some specialist centres, using allograft imported from the USA. This is difficult to arrange, expensive, and has a failure rate of 18% (Chahal et al., 2013).

3.3 Indications

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.

3.4 The Product

The product is supplied as an autologous cell therapy product of 1 to 20 million cells in a sterile syringe in autologous serum in a volume of 0.2 to 0.6ml of autologous serum as prescribed by the surgeon. A single dose is inserted at the time of surgery.

4. CLINICAL EFFECTIVENESS

Patient's symptoms improve on average by 15 to 20 points on the Lysholm self-assessment scale. Those who benefit by 12-15 months post-treatment will usually continue to benefit in the long term, at least for a decade (Bhosale et al., 2009).

4.1 Patient selection

Patients are eligible for ACI treatment if they have symptomatic chondral or osteochondral defects on the medial or lateral femoral condyle, tibial plateau, trochlea or patella that are considered suitable for treatment with ACI. Contraindications to ACI include generalised osteoarthritis with numerous osteophytes, inflammatory arthritis, anaphylaxis to products used in the manufacturing process and factors that predict a low probability of symptom relief and cannot be corrected. These may include older age, female gender or malalignment or bone loss which cannot be corrected. Contraindications which can be corrected include smoking, obesity, opiate use or the inability to comply with rehabilitation requirements.

Precipitating causes or associated conditions that could lead to advanced osteoarthritis must be corrected prior to or at the same time as ACI. This may mean including procedures such as tibial or femoral osteotomy, patellar realignment, trochleoplasty, patellaplasty, bone graft, meniscal transplantation and ACL repair.

4.2 Outcome measures

The principal outcome measure used in many clinical studies is a clinical score of pain and function. The Lysholm score is a long-established commonly used such score. We have validated an improved weighting of a self-assessment Lysholm score for patients with cartilage defects (Smith et al., 2009).

4.3 Evidence from our studies

The REACT Study

REACT, a review of our own patient cohort to 15 years, found [redacted] (See Appendix 1).

The ACTIVE Trial

ACTIVE (Autologous Chondrocyte Transplantation/Implantation Versus Existing Treatments) is a MRC-funded multicentre randomized controlled trial comparing between ACI and control treatments. The control treatments included debridement, abrasion, drilling, microfracture,

mosaicplasty, AMIC and bone graft, chosen according to the surgeon's preference. Patients could be included if they had a symptomatic chondral defect(s) on the medial or lateral femoral condyle or trochlea/patella needing surgery, which was considered suitable for ACI/MACI and at least one of the existing alternative treatments, and if a previous procedure on the same defect, carried out at least 6 months previously, had not relieved symptoms. Patients were excluded when the defect was more than 12 cm^2. Twenty-nine centres took part, enrolling 390 patients (145 in each group). The stated first primary outcome was "cessation of benefit" but this has proven difficult to measure. The second primary outcome was an independently assessed Lysholm score. According to this outcome, there was no difference between the two treatment groups during the first four years. However, at year 5 mean Lysholm score of patients treated with ACI (73.1±22.9SD) was significantly higher than that of patients in the control group (66.6±25.1SD; p=0.03).

[redacted]

An optional sub-randomization addressed the question whether two types of ACI, namely ACI using periosteum and ACI using collagen membrane, have a different clinical outcome. The evidence from this part of the trial suggests [redacted] (Appendix 2).

Studies of Repair Tissue

We have reported some correlation of clinical outcome with the graft appearance on MRI. Assessments of biopsies of our patients have found better histology in chondral defects treated with chondrocytes under a cover of Chondro-Gide® than with periosteum. Standard microscopy, immunohistochemistry and near infra-red spectroscopy studies on small tissue biopsies found the best tissue in the treated region is in the location closest to the bone in a healed defect. Substantial amounts of proteoglycan have been measured in these biopsies (see Appendix 3).

5. ADVERSE EVENTS

Serious adverse events (SAEs) were collected for all subjects enrolled into the ACTIVE trial for the first 12 months following the study intervention.

An adverse event was considered serious if it was fatal, life threatening, caused permanent disability, required hospitalisation or prolonged a hospital stay. In addition, the following were defined a requiring reporting as an SAE in the study protocol: cases of infection of the wound/joint, a fall causing causing injury and deep vein thrombosis.

Data was collected via subject questionnaires at 2 months, 6 months and 1 year post intervention. Local investigators also reported SAEs, and subject medical notes were reviewed for adverse events during monitoring visits. Relatedness was assessed by the local investigator who was not blinded to treatment allocation. All SAEs were coded using MedDRA version 17.0.

[redacted]

Table removed

Table I: Frequency and detail of adverse reactions experienced by patients treated by ACI in a multi-centre randomised trial, ACTIVE.

6. QUALITY CONTROL

6.1 Overview.

The John Charnley Laboratory provides an in-house, non-commercial clinical service, culturing autologous chondrocytes for clinicians whose patients have suffered cartilage damage. The unit was purpose built in 1999 by a specialist cleanroom manufacturer and was designed to comply with EudraLex Volume 4, Annex 1. The Laboratory is inspected by the MHRA and holds a manufacturing

licence for investigational medicinal products (licence number 21276). The detailed MHRA inspections cover both facility management and quality management.

6.2 The OsCell Program.

ACI in Oswestry remains true to the principals of the original Gothenburg procedure. Traditional ACI involves a two stage process with arthroscopic harvest followed by a cell culture period (typically three weeks) resulting in a cell suspension being used during arthrotomy. The cell suspension is injected behind a membrane which has been sutured over a cartilage defect. The wholly autologous manufacturing process involves cells being isolated from cartilage harvested by trained orthopaedic surgeons, the cells are then cultured under controlled conditions and returned to the surgeons for implantation after time in culture during which they have proliferated and have been screened for microbial contamination.

The production of biological medicinal products involves biological processes and materials and these display inherent variability, the range and nature of the products with respect to “dose” is variable but a minimum of one million cells is provided as a cell suspension. Each cell batch is patient specific. Cells are only processed from patients who have been screened negative for HIV, Hep B, Hep C, Syphilis and HTLV (Anti-HIV-1,2, HbsAg, Anti HBc, Anti-HCV-Ab, Syphilis, HTLV-I), this is in accordance with EU Directive 2006/17/EC (HTA ref 001:2006).

The manufacturing operation is carried out within a clean room suite. All procedures are performed by trained personnel in Grade A working environments (Class II microbiological safety cabinets), the background is maintained at Grade B. Throughout processing, a laser particle counter is operated, settle plates are exposed, and finger dabs are also performed. There is a documented daily, weekly and monthly cleaning regime and the clean room is annually validated by external contractors.

Harvested tissue is allocated a unique number on arrival in the facility and this number is retained to provide traceability throughout processing. Aliquots of all spent tissue culture fluids are sent for microbiological screening according to established protocols. Pre-release criteria include Endotoxin testing in addition to cell counts and viability assessment. To date, no cell batches have been lost due to laboratory acquired infection, no endotoxin tests have been positive and cell viability achieves 95-100% at return. The John Charnley Laboratory and OsCell program illustrate how the NHS can achieve a cost effective and successful provision of advanced cell therapy services.

7. COSTS AND BENEFITS

7.1 Costs

ACI is a two-stage procedure. The current costs of ACI as reimbursed to the RJAH Orthopaedic Hospital according to the National Tariff Payment System (2014/2015) is £2,398 for the first stage and £6,876 for the second stage, giving a total of £9274. Including the market forces factor (MFF), the costs are £9565. These prices include the costs of the operations and hospital stay, the autologous cells and any further required implants, such as a collagen membrane, and are irrespective of the cell manufacturer. The cells used at the RJAH Orthopaedic Hospital are cultured at its in-house cell production facility, the John Charnley Laboratory. The current costs of running this facility within the NHS amount to £4125 per ACI patient.

The current tariff costs of the comparator procedures, again as reimbursed to the RJAH Orthopaedic Hospital, are £5,642 for a Total Knee Replacement (TKR), and £2,396 for a microfracture, an osteotomy or a mosaicplasty procedure. Including the MFF, these costs are £5819 and £2471. Again, these prices are all-inclusive. Based on these current costs as reimbursed to the RJAH Orthopaedic Hospital, the incremental cost for ACI over microfracture, osteotomy or mosaicplasty is £7094. The incremental cost for ACI over TKR is £3746. Both incremental costs include the MFF.

Further data on the costs of ACI and some of its comparators (microfracture, microfracture plus collagen membrane, and mosaicplasty) was collected as part of a randomized controlled trial of ACI versus alternative surgical treatments (ACTIVE). This further data refers to personal and societal costs (out-of-pocket expenses, time off work, etcetera) and was collected using patient-maintained diaries. However, a detailed analysis of this data has not yet been finished.

7.2 Benefits

As part of the same randomized trial (ACTIVE), data was also collected on the health-related quality of life benefits of ACI and its comparators in the form of annual EQ-5D-3L health profiles. Using these profiles, and UK utility values (MVH Group, 1995), EQ-5D-3L index scores were estimated and the cumulative number of quality-adjusted life years (QALYs) calculated. A preliminary analysis of these data has been carried out by health economists at the University of Nottingham. At the time of analysis, a sufficiently large number of patients had reached the 8-year point (27 in the control and 29 in the ACI group; Table II) to allow a reasonably reliable analysis. However, too few patients had reached the 9-year point (5 in the control and 2 in the ACI group), and thus this time point will not be taken into account.

The mean EQ-5D index of both ACI and the control treatments (microfracture, microfracture plus collagen membrane and mosaicplasty)

[redacted]

Table II and Fig 1removed

[redacted]

Table III removed.

Values were calculated using area under the curve, interpolating linearly between time points. Differences in baselines EQ-5D index scores were controlled for by measuring benefit as change from baseline (Manca, 2005).

Figure 2 removed

Figure 2. Pattern of cumulative baseline-adjusted QALYs over time for the two treatment groups (control and ACI) in the ACTIVE randomized controlled trial

7.3 Incremental cost per QALY

[redacted]

[redacted]

7.4 Difference in benefits between the main comparator treatments and suppliers of cells for ACI

[redacted]

[redacted]

Figure 3 removed

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Table IV removed

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8. FUTURE DEVELOPMENTS

There are a multitude of studies worldwide working on modifications of ACI for treating chondral defects; these include sourcing cells from alternative populations (for example, adipose-derived MSCs), using alternative delivery systems including many different scaffolds (eg 1), using primary cells rather than culture-expanded cells (eg autologous bone marrow derived mononuclear cells) or applying a scaffold post-microfracture (Chondrotissue®). Many have been tried in patients but not as part of a randomised clinical trial. Below are 4 areas of development that our centre is currently working on.

8.1 ACI with alternative cell types.

In January 2014 we commenced the running of a single centre clinical trial, ASCOT, under MHRA Manufacturing and Importation Authorisation for Investigational Medicinal Products (MIA[IMP]) licence No. 21276 (EudraCT number 2010-022072-31). The trial is comparing cultured-expanded autologous Mesenchymal Stromal Cells (MSC) with chondrocytes or a combination of the 2 cell types; clinical outcome at 12 months is the primary outcome. The rationale behind the combination of cells are reports in the literature that MSCs might be favourable to chondrocytes and further reports of synergic benefits from co-culturing MSCs with other cell types. To date no other randomised clinical trial has included a combination of applied cells, as with the 3-armed design of ASCOT. An important objective of this trial is characterisation of the implanted cell populations

(growth kinetics, flow cytometry, microarrays etc) which will be correlated with clinical outcome at approximately 1 year post-treatment; it is hoped that this will help to define 'cell potency' which is required by the regulatory bodies but is actually not yet defined.

8.2 Improved patient selection.

Cell therapy may not be appropriate for all patients for a variety of reasons. Predicting those patients that will benefit most from ACI would not only improve the outcome for individual patients but would lead to a greater cost-benefit of the procedure generally and better use of health resources. Research work ongoing in our centre indicates that we may have identified a novel biomarker capable of predicting and identifying those patients who are likely to fail to respond to ACI (Wright et al, 2013a). The use of pre-operative biomarkers to guide the inclusion or exclusion of patients could prove very useful. Biomarker measurement also has the potential to guide improvement of the local homoeostasis in a joint prior to cell therapies.

8.3 Use of FT-IRIS for assessing quality of repair.

Our collaborative studies demonstrating that Fourier transform infrared spectroscopy (FT-IRIS) provides information on both the composition and structure of the repair tissue may lead to a novel and less invasive method of providing this information than the current methods that necessitate removing a small biopsy. Professor Pleshko who is based in Pennysylvania University, USA and whom we have carried out this work with, is part-way to developing a probe, the aim being that it could be used arthroscopically to provide as much information on the quality of the repair tissue, but without removing any (Hanifi et al 2013).

8.4 Use of ACI in the ankle and hip.

ACI has primarily been used in the knee joint, but may also be effective in other joints. Small numbers of patients with chondral defects in their ankles have been treated but no randomised trial has been run as far as we are aware. The patients whose ankles have been treated with ACI in our centre (n=56) show significant improvement. Analysis of the first 34 of these showed ankle scores improving from a mean of 52 pre-operatively to 70 (where 0 is worst and 100 is best) at a mean of 55 months post-treatment; the average satisfaction score was 3.4 (0 representing much worse, 4 representing extremely pleased). Our patients have continued to benefit in the longer term with follow up now out to 10 years for the first patients (Whittaker et al 2005; Johnson et al 2013). There are also reports from other centres with similar results; no adverse events are seen with this type of surgery other than post-operative pain and stiffness that lasts for approximately 2 months.

Results of the use of ACI in 16 patients in the Oscell programme with chondral defects in the hip are currently being collated for publication. Our preliminary opinion is that ACI is more challenging in this joint although our most ambitious case of ACI has been performed as a salvage procedure in the hip with very encouraging results (Akimau et al 2006). Fontana in Milan has developed an arthroscopic technique for ACI to the hip with good results in the medium term (Fontana et al., 2012). In this retrospective comparison study of 30 patients, the Harris Hip Score improved by 39 points in the ACI group compared with only 10 points in a group treated by debridement alone.

9. WIDER NHS IMPLICATIONS

The current number of ACI patients treated yearly within the NHS is relatively small. According to the most recent annual Hospital Episode Statistics (2012-2013), the number of "Open autologous chondrocyte implantation into articular structure" (code W71.4) was 147. In addition, there were 34 "Endoscopic autologous chondrocyte implantation of knee joint" (code W85.3) and 24 "Endoscopic autologous matrix induced chondrogenesis of joint" (code O19.1), which are most likely codes for matrix-assisted forms of ACI.

If ACI was to be offered by the NHS as a primary treatment then we predict the demand could be in the order of 850 cases per year on the basis that we have seen no major change in the rate of referrals to specialist hospitals, and there are difficulties in providing this type of service in general hospitals. The difficulties include the need for a licence to harvest a cartilage biopsy, the high cost of cells if no discount can be obtained from an industrial supplier of cell culture, and the difficulty of arranging a cell production facility outside a teaching or similar hospital.

10. INNOVATION

Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Regenerative medicine per se is generally considered to be innovative technology in its potential to benefit patients. ACI has been one of the most common regenerative medicines to be used in the clinic in terms of numbers of patients treated, not only in orthopaedics but also in most other specialities in medicine. Having faced the challenges and crossed the bridge from being licensed by the HTA only to being considered as a pharmaceutical product and licensed by the MHRA, it is to be hoped that it could now move forward faster. If certain changes can be made to make it more easily

and widely available to more patients, it could certainly make a 'step-change' in the treatment of the degenerate joint.

Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?

Whilst ACI has been shown to have a benefit of 1.8 QALY's, it is recognised that the EQ5D, which the calculation of the QALY is based on, is a crude assessment tool. Additional benefits which it would not pick up are the likely alleviation or delay of a joint replacement, which successful treatment by ACI would result in. Such arthroplasty is not only costly, especially if it results in a revision when performed in young patients or due to the increased longevity of the average-aged population, but also restricts the activity levels and well-being of the patients.

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

Appropriate data should become available from long term studies (these are necessary since OA with its resultant need for arthroplasty is a chronic and slowly developing condition. Indeed we have 2 on-going studies which we hope should be able to contribute to such data. One is the MRC-funded ACTIVE trial (comparing ACI with alternative treatment) with its final 10 year outcome anticipated in 2021; the other is an Arthritis Research UK-funded study, comparing the rate of development of OA in patients treated with ACI in our centre with patients treated by alternative methods (microfracture or debridement). We should have data available on that within 12 months.

11. Appendices

Appendix 1 The REACT Study

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Appendix 2 : The ACTIVE Trial

CONFIDENTIAL in entirety

Appendix 3: Studies of quality of repair (by MRI, histology and biochemical analyses)

In addition to clinical function, we and others have studied the newly formed cartilage in defects treated by OSCELL using MRI and histology of biopsies of the repair tissue.

A. Imaging

In addition to self-assessment and clinical assessment of cartilage repair procedures it is desirable to find objective means to assess the outcome of ACI or other cartilage repair procedures. Arthroscopy can directly assess the cartilage surface but is invasive and can only assess the cartilage surface. Imaging offers a non-invasive alternative.

The ideal imaging exam should be able to assess the graft, adjacent cartilage and bone and the joint overall. The best overall imaging modality for this is MRI; its only weakness being limited information on the bone part of the joint.

Conventional MRI is non-invasive, not harmful, reproducible and repeatable and is the investigation of choice in cartilage imaging. MRI can be used to assess the ACI graft, its integration to adjacent cartilage and the bone marrow deep to the graft. However it cannot assess graft histology (Tins et al 2005). There is correlation of clinical outcome with the graft appearance on MRI, though it is limited (Takahashi et al 2006, De Windt et al 2013). Generally the better the defect site has been filled with graft material and the more normal the subchondral bone on follow-up imaging the better the clinical outcome. A better quality of tissue is also seen where a patient does not have large numbers of osteophytes already present (Glaser et al., 2007). Other findings from imaging studies demonstrate that 65% of patients had complete fill of defect at 1 year post-treatment, and that changes in the subchondral bone were common with 47% showing oedema, 12% cysts and 4% sclerosis Takahashi 2006, Minas et al 2010). De Windt also found some correlation between clinical outcome and T2 index, a non invasive technique based on the MRI signal relaxation properties of tissues.

Ultimately MRI is well suited to demonstrate total graft failure and procedure complications. However in any individual patient it is difficult to accurately predict future clinical outcome from the current imaging appearance.

B. Histology

Many histological studies of repair tissue have been performed in our centre; these include evaluating the morphology of the cartilage which has formed, identifying different matrix molecules or proteases which are present, and attempting to develop new, less invasive methods of obtaining

the same amount of information. The scientific community is very interested in the quality of the tissue which forms at the site of ACI and how closely it resembles native articular cartilage, a specialised form of hyaline cartilage. The underlying belief is that a repair tissue more resembling native cartilage will have a better long term survival and better clinical results. However, histological quality of the repair tissue has not been an outcome measure in all clinical studies, partly due to the invasive nature of obtaining the necessary samples. Biopsy and histology has been performed in 50 - 60% of the patients treated in our centre and also 2 significant trials of ACI versus microfracture (Knutsen et al 2004, Saris 2008). In an effort to standardise reporting of histology, a researcher from the OsCell group, based at the RJAH Orthopaedic Hospital, instigated the setting up of the International Cartilage Repair Society (ICRS) Histological Endpoint Committee which lead to the development of a score, ICRS I (Mainil-Varlet et al 2003). This first version has now been superseded by the ICRS II Histology Score (Mainil-Varlet et al 2010). The ICRS II score is widely used in cartilage repair studies and forms part of the ICRS recommended guidelines for use in preclinical and clinical trials (Hoemann et al 2011). The use of this score with its recommendation that the full depth of the repair tissue is assessed (from the articulating surface to the attachment with the underlying bone, rather than a small portion of the repair), has resulted in the repair tissue being more commonly reported as containing some fibrocartilage than earlier studies of ACI. Another parameter of great interest is whether the type of collagen present is that most commonly found in hyaline cartilage (type II collagen) or that in fibrocartilage (type I collagen). Our study of 65 biopsies from 58 patients 8–60 months after treatment by ACI alone (n=55) or in combination with mosaicplasty (n=10), showed that the repair cartilage was 2.89±1.5mm thick, that there was good basal integration between the repair cartilage, calcified cartilage and subchondral bone (Roberts et al., 2009). Sixty five percent of the biopsies were predominantly fibrocartilage and consisted mostly of type I collagen and also contained the 'immature' form of type II collagen, IIA procollagen, 15% were hyaline cartilage (mostly type II collagen), 17% were of mixed morphology and 3% were fibrous tissue (mostly type I collagen). Type II collagen and IIA procollagen were usually found in the lower regions near the bone and most type II collagen was present 30–60 months after treatment. The presence of type IIA procollagen in the repair tissue supports our hypothesis that this is indicative of a developing cartilage, with the ratio of type II collagen:procollagen IIA increasing from <2% in the first two years post-treatment to 30% three to five years after treatment. This suggests that cartilage repair tissue produced following ACI treatment, is likely to take some years to mature (Roberts et al., 2009). There is also evidence of enzymatic activity (aggrecanase and matrix metalloproteinases) on the proteoglycan populations in the repair tissue, consistent with matrix remodelling (Roberts et al 2001).

Later studies from our group have investigated the presence of other matrix molecules, clusterin and lubricin (McCarthy et al 2013; Roberts et al 2010). These are both located at the surface of articulating cartilage and they play vital roles in normal function of cartilage.

A study has recently been published comparing clinical and histological outcome of 88 patients who had received ACI, 55 with a periosteal patch (ACI-P) and 33 with a Chondro-Gide® patch (ACI-C) (McCarthy and Roberts 2013). Within each patch type group, there was a significant improvement in Lysholm score from pre-operatively to that taken at the time of biopsy (from 39 to 52 (P=0.007) and 50 to 75 (P=0.0001) for ACI-C and ACI-P respectively), but the level of improvement at the time of biopsy and at latest follow-up (up to 13 years post-ACI) was not significantly different between the two groups. Compared with ACI-P, the repair tissue formed from patients treated with ACI-C demonstrated a significantly higher score for cellular morphology (ICRS II score), significantly better surface morphology from medial femoral condyle treated defects (ICRS II score) and a significantly higher proportion of hyaline cartilage formation (OsScore). Patients treated with ACI-C demonstrated significantly more collagen type II immunolocalisation compared to ACI-P. This was despite the patients having received ACI-C being significantly older (mean age 38.7±8.1 years) than those having received ACI-P (mean age 34.2±10.1 years) at the time of treatment (P= 0.04) and the mean size of defect treated with ACI-C being significantly larger than that treated with ACI-P (P= 0.009) and the ACI-C treated patients having a significantly lower Lysholm score pre-operatively (P=0.04). We concluded that a better quality of repair tissue formed with ACI-C compared with ACI-P, such that we suggest that Chondro-gide® should be used instead of periosteum during ACI where possible.

C. Biochemical composition

Biochemical composition has been examined using the specialised techniques of fluorophore-assisted carbohydrate electrophoresis (FACE) and fourier-transform infrared spectroscopy (FT-IRIS). These are both suitable techniques for qualitative and quantitative assessments on small samples such as the biopsies of repair tissue by necessity must be. FACE has been used to study the glycosaminoglycan (GAG) content whilst FT-IRIS has provided information on the biochemical composition (collagen and proteoglycan), as well as how the matrix is organised. Results from both of these techniques were evaluated by comparing to immunohistochemical staining of sections of the repair biopsies. FACE was used to analyse biopsies of repair tissue from 8 patients 12 months post-ACI and compare the GAG content to post-mortem age-matched samples (Sharma et al 2007).

This demonstrated that levels of chondroitin and keratan sulphate were 2-fold lower in the repair tissue compared to the age-matched controls; the profile of the repair tissue was 'younger' by comparison, with lower levels of chondroitin-6-sulphate than expected for the age of the patient.

FT-IRIS has been used by collaborators in the USA to obtain information on sections of biopsies of repair cartilage from our centre (Hanifi et al 2012, 2013). This technique applied to histological sections collected onto low-emissivity slides could, with the use of multivariate spectral models, effectively provide information on the PG content, both types I and II collagen content and the organisation of the collagen fibres, all from one 7 micron thick section. It thus provides an extremely large amount of information on a very small amount of tissue, and has the potential to improve on existing techniques.

Appendix 4: Literature Review

This section will focus on those studies reporting different types of ACI of the knee, as there are many existing reviews of ACI trials.

A review by researchers in Singapore of comparisons of different types of ACI found 7 relevant publications relating to this topic (Goyal et al 2013). They concluded there was weak evidence for superiority of ACI with a collagen membrane over the use of periosteum. They found no evidence that matrix-based ACI is better than the original ACI with periosteum. They support the use of accelerated rehabilitation with strong evidence. We have applied the same search criteria they used and found only one further subsequent publication, to give 8 publications in all, briefly described below.

(i) ACI vs MACI® for osteochondral defects of the knee (Bartlett et al 2005).

In this trial of 91 patients, 44 received ACI-C and 47 received MACI®.

In MACI® the cells have been attached within Chondro-Gide® or a similar membrane, which allows for easier handling of the cells.

There were difficulties in the randomisation process of this trial and 16 patients were excluded because despite being treated with MACI®, their lesions were in retrospect not thought suitable for MACI®. There was a significant improvement in both groups as measured by the Cincinatti score with an 18 point rise in the ACI-C group and 20 point rise in the MACI® group, but no significant difference between the groups. Arthroscopic assessment at 1 year found the ACI-C to be good to excellent in 79% of the ACI-C and 67% of the MACI® group. Hypertrophy of the graft was similar at 9% in the ACI-C group compared to 6% in the MACI® group, and re-operation was 9% in both groups. Histology of the ACI-C was reported as good to excellent in 79% compared to 66% in the MACI® group. This study found that patients with previous surgery in the form of a mosaicplasty or a carbon-fibre implant, or multiple previous surgeries, had a 25 point lower Cincinatti score post-operatively of only 35. There were no graft failures in the ACI group, but two failed in the MACI® group.

We conclude that the main advantage of using MACI® is the ability to do the procedure more quickly than ACI. We see no evidence that its use gives superior clinical results compared to ACI.

(ii) Randomised trial of ACI with Periosteum versus ACI with Chondro-Gide®(Gooding et al 2006).

This randomised trial compared the use of periosteum against a collagen membrane. There was improvement in both groups, with a 2 year Cincinnati functional score of good or excellent in 66% of

the periosteum group and 74% of the Chondro-Gide® group. 36% of the ACI-periosteal patients required shaving of hypertrophic growth at one year compared with none of the Chondro-Gide® grafts. We note this trial ran from March 1999 to February 2002 and was soon after the introduction of ACI to that centre. We know it is difficult to harvest a thin layer of periosteum and this may have impacted on the outcome of the study. Our centre moved to the use of Chondro-Gide® in place of a periosteal patch in 2002. The high rate of re-operation in the Gooding study may also be related to the type of rehabilitation used at that time. A later trial from the same institution that ran from February 2002 to April 2003 used accelerated rehabilitation regimes and reported 9% rates of hypertrophy (Bartlett, 2005).

(iii) ACI with periosteum versus MACI® (Zeifang 2010)

This randomised clinical trial in Germany was on only 21 patients with an average age of 29. It did however find a statistically significantly better improvement in ACI with periosteum over matrix associated ACI, despite the small numbers in the trial. The Lysholm score rose to 86 at 12 months in the ACI group compared with 76 in the M-ACI group. It should be noted that this M-ACI differs in some respects from the MACI® provided by Genzyme (and later Sanofi) as the matrix used was of polygalactin and polydioxanone rather than collagen.

We conclude that M-ACI with the material used is significantly inferior to ACI with periosteum.

(iv) ACI with periosteum compared with ACI with a collagen membrane (Samuelson, 2012)

This health-economic study in Nebraska, USA, was designed to address the issue of an increasing use of a collagen matrix in the USA where only periosteum is licenced for use. The main manufacturer of a collagen matrix has not sought FDA approval as the cost of obtaining approval is so high, and the use relatively specialised. The membrane is thus used 'off-label'. Surgeons in the USA are able to use devices 'off-label' in a manner supported by the FDA.

This study found ACI with a collagen membrane to be more cost-effective at $9243 per QALY than ACI with periosteum at $9466. An appropriate amount of theatre time and cost is included in the calculation. As part of the study they compared the reported rates of graft hypertrophy from various studies and found it to be 25% for ACI with periosteum compared to 10% for ACI with a collagen membrane.

(v) ACI in two age-groups (Neimeyer 2010)

In this study ACI was performed with a collagen membrane that was loaded with chondrocytes just for 10 minutes before implantation. This is slightly different from MACI®, where cells are cultured in

the membrane in the cell production facility for 1 to 2 days prior to implantation. The aim was to compare a younger with an older group and the older group aged from 40 to 57 years. The rise in Lysholm score was 20 points at 1 year with no significant difference in those under 40 years compared with those over 40 years.

(vi) A randomized trial comparing accelerated and traditional approaches to post-operative weight-bearing (Ebert 2012)

This study compared between standard rehabilitation to full weight bearing at 11 weeks and accelerated rehabilitation to full weight bearing at 8 weeks. There was less pain, a longer 6-minute walking distance and improved knee extension range at all periods up to 2 years. At five years, the only difference between the two groups was less frequent pain in the accelerated rehabilitation group.. No attributable adverse effects of accelerated rehabilitation were found.

(vii) ACI with accelerated rehabilitation (Wondrasch 2009).

In this randomised trial all patients had MACI® but in one group rehabilitation encouraged full weight bearing at 6 weeks compared to 8 weeks. Less knee effusion was seen in the more active group. No significant difference in clinical function improvement was seen at 2 years, but only 31 patients were in the study and so there may be benefits that could not be measured. From our own experience we consider it is likely that small improvements in selection, in technique and in rehabilitation will be developed in coming years, and improve the outcome of ACI.

(viii) ACI in the knee. Mid to long-tem results (Nawaz, 2014)

The group in Stanmore has used a range of different techniques over the years, including ACI with periosteum, ACI with collagen membrane and ACI as MACI®. This audit was able to look at results in 827 patients out of 1000 cases performed out to 12 years from implantation. The cohort of patients with MACI® was subsequent to the group with ACI and the study does not make an analysis of outcome with time as a controlled variable. Generally most centres learn over time how to optimise patient selection, a particular surgical technique, and rehabilitation. The Nawaz paper reports on failure rates, with failure defined as failure defined as any of the following: (1) graft delamination proven either by MRI or arthroscopy; (2) a new surgical intervention, including arthroplasty, high tibial osteotomy, or another revision procedure (graft hypertrophy was not counted as a failure); (3) a VAS pain score within less than 2 points of the preoperative score; or (4) a Stanmore functional score that was the same or worse than the preoperative score. According to this definition, the cumulative failure rate at 10 years for both types of procedures was 51%, with no difference

between them (p=0.68). We therefore do not see evidence in their report to support either MACI® or ACI as superior.

The risk of failure was significantly higher in the older patients and in those with more severe joint degeneration as assessed by the Kellgren-Lawrence grading system, a system strongly relying on loss of joint space and formation of osteophytes. These findings confirm our own observations (Takahashi et al 2006; Bhosale et al., 2009). Failure was less likely for lesions in the lateral compartment, and where there had not been previous cartilage repair procedures.

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