NICE National Institute for Health and Care Excellence

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

Assessment Report

Commercial in Confidence stripped version for consultation

Produced by: Warwick Evidence

CONFIDENTIAL UNTIL PUBLICATION

Autologous chondrocyte implantation in the knee

Source of funding: This report was commissioned by the NIHR HTA Programme as project number HTA 13/65

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Date completed: 2nd December 2014

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme.

Conflict of interest: None

This report should be referenced as follows:

Mistry H, Shyangdan D, Clar C, Court R, Royle P, Biant L, Waugh N. Autologous chondrocyte implantation in the knee. *Health Technology Assessment 2015*

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Acknowledgements

We thank Peter Auguste for helping with transition probabilities.
We thank the following the advice but absolve them from any responsibility for the final report;
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List of abbreviations

ACI	Autologous chondrocyte implantation
ACI-C	ACI - collagen cap
ACI-P	ACI – periosteal flap
ACTIVE	Autologous Chondrocyte Transplantation/Implantation Versus Existing Treatment
AE	Adverse event
BASK	British Association for Surgery of the Knee
BMI	Body mass index
CC	ChondroCelect
CCI	Characterised chondrocyte implantation
CCT	Controlled clinical trial
CEAC	Cost-effectiveness acceptability curve
CGI-E	Clinical global impression measures of efficacy
CGI-I	Clinical global impression measures of improvement
CHEERS	Consolidated health economic evaluation reporting standards
CI	Confidence interval
CPV	Continuous passive motion
CRD	Centre for Reviews and Dissemination
CUCS	Compassionate use case series
DVT	Deep vein thrombosis
EMA	European Medicines Agency
EPAR	European public assessment report
EQ-5D	EuroQol-5D
EQ-5D-3L	EuroQol-5D-3L
ERG	Evidence review group
FDA	Food and drug administration
FU	Follow up
GP	General practitioner
HCHS	Hospital and Community Health Services
HR	Hazard ratio
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ICRS	International cartilage repair society

IKDC	International Knee Documentation Committee
KM	Kaplan Meier
KOOS	Knee injury and osteoarthritis outcome
MACI	Matrix induced chondrocyte implantation
MSAC	Medical Services Advisory Committee
MF	Microfracture
MFF	Market forces factor
MRI	Magnetic resonance imaging
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NR	Not reported
NRIG	No re-intervention group
NSAID	Non-steroidal anti-inflammatory drug
OA	Osteoarthritis
OAT	Osteochondral autograft transfer
OATS	Osteochondral autograft transfer system
OCD	Osteochondritis dissecans
ONS	Office for national statistics
PbR	Payment by result
PKR	Partial knee replacement
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PSS	Personal social services
QALY	Quality adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RJAH	Robert Jones and Agnes Hunt (Hospital, Oswestry)
RIG	Re-intervention group
RR	Relative risk
SA	Sensitivity analysis
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SF-36	Short Form-36
SUMMIT	Superiority of Matrix-induced autologous chondrocyte implant versus Microfracture for Treatment of symptomatic articular cartilage defects

TA	Technology appraisal
TEAE	Treatment emergent adverse event
TKR	Total knee replacement
TTF	Time to treatment failure
VAS	Visual analogue scale
WORMS	Whole organ MRI score

Scientific summary

Background

The surfaces of the bones in the knee are covered with articular cartilage, a rubbery-like substance that is very smooth, allowing frictionless movement in the joint, and acting as a shock absorber. The cells that form the cartilage are called chondrocytes. Natural cartilage is called hyaline cartilage.

Articular cartilage has very little capacity for self-repair, so damage may be permanent. Various methods have been used to try to repair cartilage defects in the past, usually aiming to replace the damaged cartilage using bone marrow cells including stem cells, which then form a tissue called fibrocartilage. The commonest way of doing this is called microfracture. Small holes are drilled through the bone underlying the damaged area to allow the marrow cells to fill the defect. Microfracture (MF) is a useful procedure that has benefitted many people, but the fibrocartilage formed is less durable than natural hyaline cartilage, and repairs wear out over the years. Autologous chondrocyte implantation (ACI) is a two-stage procedure which aims to replace the damaged cartilage with hyaline cartilage. In the first stage, a small piece of articular cartilage is taken from the knee, and the cartilage producing cells, known as chondrocytes are cultured in the laboratory, until there are millions of cells. These cells are then implanted into the damaged area.

The methods of ACI have been evolving. In the first generation of ACI (ACI-P – p for periosteum), the cultured cells were implanted into the defect, as a liquid suspension, and then covered with a cap made from periosteum – the tough fibrous tissue that covers bones. This required a procedure to harvest the periosteum, which caused some discomfort to the patient afterwards.

In second generation ACI, the periosteal cover was replaced by a collagen cover (ACI-C for short), but the cells were still in liquid suspension, and the cover still had to be stitched in place.
One development in ACI has been “characterisation”, a process in which the cells with the best ability to form hyaline cartilage are selected during culture.

In the third generation of ACI, the cells are seeded or loaded into a collagen membrane, rather than being in a liquid suspension with a cap. The membrane is then implanted into the defect. This is usually referred to as MACI. We use ACI without suffix or prefix to cover all forms.

Decision problem

The scope from NICE for this appraisal mentions three forms of ACI;

- The ChondroCelect ACI system from TiGenix, in which the cultured cells are combined with a biodegradable collagenI/III patch. This is a form of characterised chondrocyte implantation (CCI).
- The Matrix ACI system (MACI – short for "matrix applied characterised autologous cultured chondrocyte implant") now marketed by Vericel. MACI is often used as a generic term so we will use MACI® when referring to the Vericel product.
- ACI wherein the cells are cultured in hospital or research laboratories, such as the Robert Jones and Agnes Hunt (RJAH) Hospital in Oswestry, termed "traditional ACI" in the NICE scope. This appears to be the only NHS facility that currently cultures cells for use in ACI. Traditional ACI is used under hospital exemptions from the advanced therapy medicinal products regulations.

The main comparator is microfracture. We assumed that conservative, non-surgical treatments such as physiotherapy would be tried first, and so would not be a comparator, in line with the [redacted]

Clinical effectiveness

We first carried out a review of existing systematic reviews, focusing on those that assessed the comparative effectiveness of various forms of ACI and microfracture. We then searched for recent trials, focusing on those that used the most recent forms of ACI.

The outcome measures used in ACI 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 reviews were mostly inconclusive on the choice between ACI and microfracture, for reasons that include poor quality of primary studies, the hetereogeneities of patients recruited, ACI methods used, and outcome measures, variations in previous surgery, and short follow-up periods.

Four RCTs published since the last appraisal provided evidence on the efficacy of ACI in patients with symptomatic cartilage defects in the knee. Two studies, one by Basad and colleagues with 60 patients, and the SUMMIT trial by Saris and colleagues with 144 patients, compared MACI® (both

Genzyme) against MF. The TIG/ACT/01/2000 trial (hereafter TIG/ACI trial) with 118 patients compared ACI-P with characterised chondrocytes against MF. The ACTIVE trial

[redacted] Three studies were of good quality while the remaining one had to be rated as poor mainly due to inadequate reporting.

Patients were followed up for two years in both MACI® studies. The primary outcome measures in the trial by Basad and colleagues were Tegner and Lysholm scores. Lysholm scores improved in both MACI® and MF groups from baseline to 12 months (MACI 52 at baseline, 95 at 12 months vs. MF 55 at baseline, 81 at 12 months), but the improvement was maintained to 24 months only in the MACI® group (92 vs. 69, p=0.005). Tegner scores improved from baseline in both groups but more so in the MACI® group (MACI level 2 to level 4 vs. MF level 2 to level 3; p=0.004).

In the SUMMIT trial the main outcomes were change in KOOS pain score and function from baseline to year 2. The mean improvements in KOOS pain score and KOOS function score from baseline to end of follow up were statistically significantly greater in the MACI® group than in the MF group. Similarly, the proportion of responders was significantly higher in the former with more non-responders in the latter. Factors that predicted positive response to MACI® were male gender, a median age of <34.5 years, presence of a single lesion which occurred due to acute trauma, history of only one previous surgical procedure, symptoms for >3 years and lesion of size >4 cm^2 located on the femoral condyle. Two patients in the MF group and none in the MACI group failed treatment. More patients in the MF group reported adverse events, most frequently arthralgia.

In the TIG/ACT trial of ChondroCelect, patients were followed up for 5 years. The primary outcome measure was change in overall KOOS score from baseline at 36 months and 60 months. There was improvement in the overall KOOS score at 60 months with both treatments. The difference between the two was not statistically significant. Patients with onset of symptoms <3 years duration had better improvement with ACI-P. Seven patients in the ACI-P group and ten patients in the MF group failed treatment. More patients in the ACI-P group experienced at least one adverse event but they were mild to moderate in intensity. The most commonly reported adverse event was arthralgia.

The ACTIVE trial compared ACI (including ACI-P, ACI-C, and MACI) against standard treatments (MF, abrasion, drilling, mosaicplasty). The primary outcome measure was Lysholm assessor score. [redacted]

[redacted]

A number of studies suggest that ACI done in patients who have had previous microfracture is less successful than if it is done as first repair, because microfracture damages the subchondral bone.

Cost-effectiveness

Review of previous economic studies

We carried out a systematic review of existing economic evaluations of the use of ACI, MF and mosaicplasty for repairing symptomatic articular cartilage defects of the knee. A broad search was done in Medline, Embase, NHS EED and Web of Science, for studies published since the last HTA review in 2005.

Studies were considered relevant if they were full economic analyses (including economic models) on the use of ACI, MF and mosaicplasty for repairing symptomatic articular cartilage defects of the knee. We checked 272 abstracts and found 6 relevant articles (including two technology assessment reports). All articles had shortcomings, most notably the lack of long-term clinical follow-up data and the lack of good quality of life data (utility data).

Review of submissions received

We also reviewed the submissions from Swedish Orphan Biovitrum on ChondroCelect, from Aastrom Biosciences on MACI®, and from OsCell, including unpublished data from the ACTIVE trial.

Swedish Orphan Biovitrum AB developed a *de novo* Markov economic model – only the written assessment was given to the ERG and no electronic model was provided to support this written assessment. Their modelling assumed that microfracture was the comparator, that if the first repair fails patients can have a second repair but only with MF, and that the main driver was time to failure of the first repair. They used data from the TIG/ACT trial. Their key assumptions were that fewer patients who had ACI needed second repairs and that they had a longer duration of success, thereby postponing the need for knee replacement. Their base case ICER was about £9,000 per QALY.

Aastrom did not provide any cost-effectiveness analyses due to the recent purchase of the MACI® product from Sanofi but did provide a budget impact/costing forecast. They explored two scenarios,

one with MACI® or ACI as first procedure, and the other with MF. Based on data on failure rates from the SUMMIT trial, they estimated that there would be cost-savings from using MACI® due to the lower need for further repairs.

The Oswestry group provided a prospective cost-effectiveness analysis for the ACTIVE trial but did not provide an economic model. This analysis used quality of life (EQ-5D-3L) data based on up to 8 years of follow-up. It assumed a cost for cells of only £4125, based on production by OsCell [redacted]. It is not clear how the reported EQ-5D results were converted to QALYs. [redacted].

New modelling

We constructed a lifetime Markov model, starting with a cohort of people aged 33 years with symptomatic articular cartilage defects of the knee who required either an ACI or MF. The main comparison was between ACI and MF, and the analysis considered the need for subsequent events including further repairs and later knee replacements. Most patients (87.5%) did not need a second repair. We created two scenarios to allow direct comparisons: in scenario 1, all second repairs were ACI and in scenario 2, all second repairs were MF. Secondary analyses considered other options, including ACI after prior MF.

For the base-case analysis, for the knee repairs we used data mainly from the TIG/ACT trial of ChondroCelect and the SUMMIT trial of MACI®, both of which compared ACI with microfracture. For knee replacement, we used data from published literature.

The results indicated that ACI is more cost-effective than MF as a first repair, and that if a second repair is needed this should also be ACI. The base-case discounted ICER for ACI compared to MF was just over £14,000 per QALY for scenario 1 and was just under £16,000 per QALY for scenario 2.

Results from the different sensitivity analyses were in line with the base-case results. ICERs ranged from £2,779 (scenario 1) or £3,016 (scenario 2) for a 75% cell cost reduction to £25,992 (scenario 1) or £27,388 (scenario 2) for a 10 year time horizon. We carried out further analyses using utility data from the ACTIVE trial, using costs of both commercially produced cells and OsCell ones. [redacted]

The key drivers in the base case were the cost of cells for ACI and the relative durations of benefit from ACI and MF. After the first few years (varying amongst studies) ACI was more beneficial (more gain in QALYs) and led to cost savings to the NHS (fewer people in need of a second repair or of a TKR, and first TKR postponed reducing the need for second TKR).

Limitations in the economic analyses included uncertainties with long-term progression rates and quality of life (utility) data. However, longer-term data from the ACTIVE trial will provide useful information in the future.

Strengths and limitations in evidence

We now have longer term follow-up than was available for previous appraisals, and data from several new trials. In particular, the ACTIVE trial has data on some patients to 8 years and will eventually have 10 years of follow-up on all. The TIG/ACT trial has five years of follow-up. However the two trials of MACI® against microfracture have currently only two years of follow-up. The limitations are that the technology is evolving, and the longest term data come from versions of ACI which are superseded. For example, the TIG/ACT trial used ACI with a periosteal cap, as did the early years of the ACTIVE trial. ACI-P requires more follow-up procedures and hence incurs extra costs compared to ACI-C. The ChondoCelect cells are now used in a MACI procedure.

Most, but not all, studies suggest that ACI is more effective if used soon after the cartilage injury. Our modelling using Oswestry utilities gave a different conclusion to the Oswestry analysis for reasons which cannot entirely be explained by the different assumptions about costs of cells.

We used a cell cost of £16,000 in line with published prices, but we are aware of discounted prices which seem to vary by time and place. We have addressed this by sensitivity analysis.

Conclusions

The evidence base for ACI has improved since the last appraisal by NICE. In most analyses, the ICERs for ACI compared to microfracture appear to be within a range usually considered acceptable.

1 Chapter 1

1.1 History

The first appraisal of ACI was in 2000, after which NICE issued TA 16 (December 2000)[1] wherein the guidance stated that;

1.1 Autologous cartilage transplantation is not currently recommended for routine primary treatment of articular cartilage defects of the knee joint in the NHS.

1.2 ACT should only be performed as part of a properly structured trial which wherever possible is randomized and adequately powered."

This decision was made because there was then no evidence from randomized controlled trials (RCTs). The available evidence came from 17 case series of different interventions, and NICE concluded that;

"Assessment of the evidence on clinical efficacy is confounded by a number of factors including variations in patient characteristics, concomitant surgery and use of multiple interventions. With one exception, all studies reported an improvement in patient status, usually over a follow-up period of less than 2 years."

These studies are summarised in the report by Jobanputra and colleagues.[2] The studies lacked control groups, without which it is difficult to assess the effectiveness of procedures, relative to natural history or alternative treatments.

The guidance was reviewed in 2005, supported by a report by Clar et al.[3] The guidance issued as TA89 stated that

"Autologous chondrocyte implantation is not recommended for the treatment of articular cartilage defects of the knee joint except in the context of ongoing or new clinical studies that are designed to generate robust and relevant outcome data, including the measurement of health-related quality of life and long-term follow-up."

The terminology had changed. The initial term of autologous cartilage transplantation had been replaced by 'autologous chondrocyte implantation' (ACI), which is more correct for two reasons. First, the small group of cells removed is multiplied before being put in, so transplantation is not correct because what goes back in was not what came out. Second, what is implanted is cells (chondrocytes) rather than cartilage, which takes time to develop.

The evidence base had improved by 2005, with four RCTs, two comparing ACI with mosaicplasty,[4, 5] and two comparing it with microfracture.[6, 7] The duration of follow-up was still short. At two years, there appeared to be little difference between ACI and mosaicplasty or microfracture. In the absence of long-term data, it was not possible to produce reliable costs per QALY.

This report is written to support the third NICE appraisal of ACI in the knee.

1.2 Background

Articular cartilage covers the ends of the bones, and the inner surface of the patella, in the knee joint. It should not be confused with the meniscal cartilages that are cushions of cartilage between the bones – when people talk of "cartilage problems" in the knee, they often mean the meniscal cartilage. Normal hyaline cartilage is a rubber-like substance that is normally very smooth, promoting smooth frictionless movements of the joints and also acting as a shock absorber. It is formed mainly of a protein called type 2 collagen. Under the articular cartilage are the bones of the knee – femur in thigh, tibia below the knee and the patella or knee-cap.

Cartilage has no blood vessels and has very limited ability to repair itself. Epidemiological studies show a relationship between knee injury and later development of osteoarthritis. In some people, this will lead in the long-term to a need for a knee replacement with an artificial joint.

Loss of articular cartilage is referred to as a chondral defect, and loss of cartilage and bone as an osteochondral defect.

Cartilage damage can be caused directly from injury, by various types of arthritis, or spontaneously in a condition called osteochondritis dissecans (OCD). Cartilage damage may also arise because of knee instability or abnormal loading, for example secondary to a ligament injury [8] or damaged meniscal cartilages.[9] Serious obesity may also affect knee cartilage.[10] Conversely, physical activity without injury may be protective.[11]

In young people the most common cause of hyaline cartilage damage is sporting injuries. Aroen and colleagues reported the causes of injury in patients having knee arthroscopy in Norway over a 6-month period.[12] Injuries occurred in sport in 55%, in the home in 15%, at work in 12% and in road traffic accidents in 5%. In 13% the cause was unknown.

It should be noted that cartilage defects without any underlying bone involvement may not cause pain – there are no nerves in cartilage. The source of pain in knees with damaged cartilage is poorly understood but may come from many sources including ligaments, the joint capsule and the underlying bone.[13] So results from series of symptomatic patients may not be entirely representative of all people with cartilage damage. The commonest symptom is pain, with others being temporary locking of the knee in one position, and swelling. Pain and disability from symptomatic cartilage lesions has been shown to be as significant in magnitude as that from severe arthritis of the knee.[14]

The International Cartilage Repair Society (ICRS) has a scoring system for grading the severity of cartilage damage[15];
Grade 1: soft indentation and/or superficial cracks
Grade 2: small cracks or lesion extending down to under half of cartilage depth
Grade 3: deep cracks or gaps of over 50% of cartilage depth
Grade 4: cracks through the total thickness of cartilage down to the underlying bone
Grade 5: defects of the full thickness of cartilage involving the sub-chondral bone

Grading has to be done by arthroscopic examination.

1.3 Interventions

1.3.1 Lavage and debridement.

In lavage, the arthroscope (a sort of fibreoptic telescope) is inserted into the knee and saline is poured in through a cannula. This is usually done under general anaesthesia on a day case basis. The saline washes out loose debris through the cannula. It is also thought to wash out compounds that cause inflammation.

Debridement is done under arthroscopic vision and is the removal of damaged cartilage or bone. Debridement and lavage are often done at the same time.

The evidence for effectiveness is sparse and mixed. One three-armed RCT of lavage alone, lavage plus debridement and a sham arm reported no difference at 2 years.[16] Another by Hubbard had methodological weaknesses, but reported that debridement and lavage was better than lavage alone.[17] The NICE intervention procedures guidance (IPG230) noted uncertainty about the efficacy of the procedure.[18]

1.3.2 ACI

Cartilage cells are called chondrocytes. In autologous chondrocyte implantation (ACI), a small piece of cartilage is removed from the knee, and the chondrocytes are grown in the laboratory until they number millions. They are then put on to the damaged area of articular cartilage as a patch. The hope is that this patch will repair the damaged area and form a new layer of natural articular cartilage, called hyaline cartilage.

ACI has been used for many years (since at least 1987[19]) and the procedure has evolved over time. The Dutch Orthopaedic Association has provided a useful summary of developments.[20] In the first generation of ACI, the cultured chondrocytes were placed in the defect, in liquid form, and then covered with a cap made from periosteum – ACI-P. This led to problems with pain in the immediate post-operative period, and a need for further procedures to remove overgrowth in the graft, as described in Box 1.

Box 1. Clinical features of ACI-P

The periosteal patch was traditionally harvested via a 3-4cm incision on the subcutaneous border of the proximal medial tibia. Careful dissection is performed to develop a plane between the periosteum (outer lining of bone) and overlying fat and fascia (outer lining of muscle). A slightly oversized patch is then harvested with a sharp surgical blade. This procedure takes approximately 30 minutes to perform and patients suffer from additional pain and swelling post operatively. Potential complications include surgical site infection, and haematoma formation at the harvest site. If an infection does occur they are treated with a one-week course of oral antibiotics.

The most common complications at site of implantation are graft overgrowth (hypertrophy) and scarring (arthrofibrosis) following this procedure. Overgrowth typically occurs between 3-6 months after the operation and results from abrasion of the patch against internal structures in the knee. This can occur in up to 50% of cases, with a significant proportion requiring further keyhole surgery to debride ("shave off") the excess tissue from the surface of the patch.[21] Furthermore, suturing the patch may damage the native surrounding cartilage, as sutures are passed through normal healthy cartilage to ensure a watertight seal for the chondrocytes.
Contributed by Mr A Sprowson, orthopaedic surgeon.

The second generation of ACI used a collagen cap (ACI-C) instead of the periosteal one, but still used cells in a liquid. Gomoll and colleagues compared two cohorts, one which had a periosteal patch (ACI-P) and one which had a collagen cap (ACI-C).[22] The re-operation rates were 26% and 5% respectively. ACI-P is now little used in the UK, but is still used in the USA, where none of the

membranes or scaffolds used in second generation ACI have yet been approved by the FDA except for in trials.[23]

In the third generation of ACI, the chondrocyte cells are loaded or embedded, or "seeded", on to a porcine collagen membrane ACT-C (autologous chondrocyte transplantation seeded collagen membrane) or matrix (MACI – matrix induced chondrocyte implantation), with a patch cut to fit. These patches can be implanted by a less invasive form of surgery, by arthroscopy or mini-arthrotomy, requiring less surgical time than ACI-C.[24] (Arthrotomy = opening of a joint). ChondroCelect cells are now used in this way, with cells being loaded into the membrane by the surgeon.

The membrane used in MACI is composed of type I/III collagen, with a rough side wherein the chondrocytes are seeded and a smooth side which faces into the joint cavity.[24] The membrane is tough enough to be cut to shape or stitched in place, though it is more often glued in place.[24] The membrane is bio-degradable. The term "scaffold" is often used instead of membrane. However the membrane needs careful handling to minimize chondrocyte death during implantation.[25]

Another development, which can apply to both second and third generation ACI, has been that only selected chondrocytes are used – this is called characterized chondrocyte implantation or CCI. Cells most likely to produce hyaline cartilage with predominantly type II collagen, rather than a less resilient cartilage called fibro-cartilage which produces mainly type I collagen[26], are identified during CCI by using a panel of biomarkers, including collagen. Tigenix used six biomarkers and Genzyme-Sanofi also used additional assays in CCI.[27]

Box 2 summarises the generations of ACI. (NB different authors use "second generation" in different ways.) It is worth noting that graft hypertrophy can occur with second and third generation ACI. Niethammer and colleagues[28] reported graft hypertrophy on MRI in 11 of 44 patients who had MACI (Novocart) and in the ACTIVE trial (Oswestry submission table 8) [redacted]

Box 2. The evolution of ACI

First generation	ACI-P. Liquid suspension of cultured chondrocyte cells placed in the defect covered with a cap made from periosteum.
Second generation	ACI-C. Liquid suspension of cells placed in the defect and covered with a collagen cap.
Third generation	The cultured cells are seeded on to a membrane or "scaffold" as in MACI (matrix associated chondrocyte implantation).
Characterized chondrocytes	Not all chondrocytes are equally good at producing cartilage. Some are more "chondrogenic" (cartilage-producing) than others. The most useful can be selected and are known as "characterized".
Fourth generation	Newer developments include the implantation not of cells that will form cartilage, but of tissue-engineered cartilage grown from autologous chondrocytes in collagen gel in the laboratory.

Harris carried out a systematic review of failures and complications after ACI and reported that failure rates were higher with first generation ACI-P than with second-generation ACI-C.[29]

The Medical Services Advisory Committee (MSAC) report concluded that the ideal application of ACI would be in a full thickness chondral defect surrounded by health cartilage in an otherwise healthy knee.[30]

1.3.3 Microfracture

The main alternative method of repair is called microfracture, in which small holes are drilled through the surface of the bone in the area of damaged cartilage. This allows bleeding from the bone marrow, and the blood carries stem cells into the area where the damaged cartilage has been debrided. These cells form scar cartilage called fibrocartilage, composed of type 1 collagen. This is regarded as being inferior to hyaline cartilage, being less hard-wearing and it is not expected to last as long.[31]

Microfracture may be combined with the insertion of a collagen membrane to cover the microfracture clot, known as augmented microfracture.

Microfracture can be done arthroscopically (i.e. without opening the knee joint) and could be done at the same time as washing out a knee joint and stabilizing loose tissue (debridement and lavage).
A search of the NICE website found no guidance on microfracture.

1.3.4 Mosaicplasty

Another method, which is now much less common, is mosaicplasty (sometimes called OATS – osteochondral autograft transfer system) involves transplanting small sections of cartilage and underlying bone from a less weight-bearing part of the knee into the damaged area. The pieces are in little cylinder shapes and once transplanted, have an appearance not unlike a mosaic – hence the name. 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. (In some countries, allograft cadaver donor tissue is used, but this does not appear to happen in the UK.)

Mosaicplasty was reviewed by NICE through the Interventional Procedures Programme.[32] The guidance is reproduced in Box 3. It was dated March 2006 so may now be out of date.

Box 3. NICE Guidance

Guidance

1.1 Current evidence suggests that there are no major safety concerns associated with mosaicplasty for knee cartilage defects. There is some evidence of short-term efficacy, but data on long-term efficacy are inadequate. In view of the uncertainties about the efficacy of the procedure, it should not be used without special arrangements for consent and audit or research.

1.2 Clinicians wishing to undertake mosaicplasty for knee cartilage defects should take the following actions.

- Inform the clinical governance leads in their Trusts.
- Ensure that patients understand the uncertainty about the procedure's efficacy and the options for alternative treatments. They should provide them with clear written information. In addition, use of the Institute's information for the public is recommended.
- Audit and review clinical outcomes of all patients having mosaicplasty for knee cartilage defects. The Institute may review the procedure upon publication of further evidence.

Mosaicplasty appears to be little used now. In the ACTIVE trial[33] (described in detail in chapter 4) of ACI versus standard methods such as microfracture and mosaicplasty, few surgeons chose mosaicplasty.

1.3.5 Conservative management

Another option is no surgical treatment. Three case series [34-36] reported high levels of return to activities after cartilage injuries after 14 year, 9 years and 9 years respectively. Messner and

Maletius reported a case series of young athletes (mean age 25, range 14-38) who had no treatment. 14 years later, most (21 out of 28) had returned to activity and 22 had excellent or good function.[34] However despite lack of symptoms, most showed radiological changes suggestive of early osteoarthritis.

[redacted]

1.4 Decision problem.

The scope from NICE for this appraisal mentions three forms of ACI;

- The ChondroCelect ACI system from TiGenix, in which the cultured cells are combined with a biodegradable collagenI/III patch. This is a form of characterised chondrocyte implantation (CCI). ChondroCelect received European marketing authorisation in October 2009.[37] It is marketed by Swedish Orphan Biovitrum. Production is being taken over by Pharmacell.[38]
- The Matrix ACI system (MACI® – short for "matrix applied characterised autologous cultured chondrocyte implant") from Sanofi. The matrix refers to a collagen membrane with the chondrocytes. The Sanofi MACI was approved in Europe in June 2103.[39] This product is now being marketed by Aastrom Biosciences who are changing their name to Vericel. MACI is used both to refer to third generation ACI, and as a trade name. When referring to the trade name, we will use MACI®.
- ACI wherein the cells are cultured in hospital or research laboratories, such as the RJAH Hospital in Oswestry, termed "traditional ACI" in the NICE scope. This appears to be the only NHS facility that currently cultures cells for use in ACI. Traditional ACI is used under hospital exemptions from the advanced therapy medicinal products regulations.

ACI is much more expensive than microfracture. The Australian Medical Service Advisory Committee estimated the cost of ACI to be about 10 times that of MF.[30]

The first decision to be made by NICE is whether ACI, in some or all of its forms, is clinically effective and cost-effective, and should now be used in routine NHS care. Both ChondroCelect and Vericel MACI® have marketing authorisations, with slightly different indications. (Box 4).

Box 4. Licences for Chondrocelct and Verigen MACI®

ChondroCelect has a UK marketing authorisation for the "repair of single symptomatic cartilage

defects of the femoral condyle of the knee (International Cartilage Repair Society [ICRS] grade III or IV) in adults". The randomised controlled trial that supported the marketing authorisation for Chondrocelect included patients with lesions between 1-5cm².[37]

Vericel MACI® 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 3-20 cm^2 in skeletally mature adult patients.[39]

It is not clear from the EMA website whether ChondroCelect is approved for lesions smaller than $1cm^2$.

The final scope for this appraisal did not consider sequencing of different technologies for the repair of cartilage defects, but the place of ACI in the treatment pathway needs to be examined. Should the much less expensive microfracture (MF) be tried first, with ACI reserved for MF failures? Or are the best results with ACI achieved if it is the first treatment for chondral defects?

There may also be a question about how soon cartilage defects should be treated. In a randomised trial of ACI versus microfracture, outcomes were better in those treated within three years of symptom onset compared to those with longer duration.[40]

Mithoefer and colleagues have also reported better results with ACI sooner after injury, in football players.[26] Harris and colleagues also concluded that results were better in patients with shorter duration of symptoms and fewer prior procedures.[41]

So there may be a case for recommending earlier ACI.

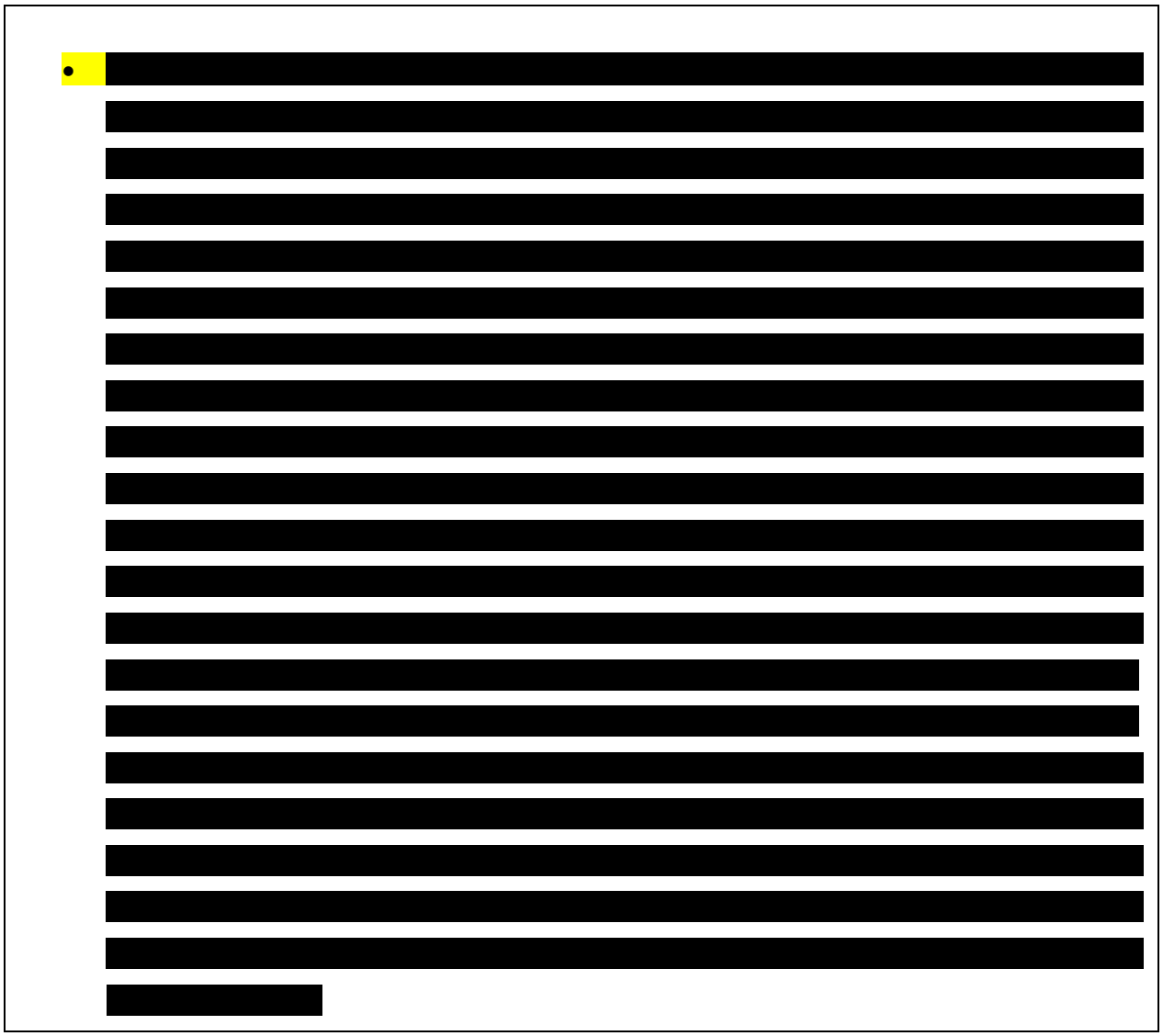
Patient group.

The patient group, as stated in the final scope from NICE, is "adults with a symptomatic cartilage defect (chondral defect) but without advanced osteoarthritis". The chondral defects can be on the femur, tibia or patella. ACI is used in other joints, but such use is outwith the scope of this appraisal.

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.

Following a UK Cartilage Consensus meeting in March 2104, a draft document with consensus statements has been circulated for comment, including to members of the British Association for Surgery of the Knee (BASK). The points most relevant to this appraisal are summarised in Box 5. The contents are academic in confidence meantime and there may be changes in the final version.

Box 5. Consensus statements from UK Cartilage Consensus meeting March 2014



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2 Chapter 2. Clinical effectiveness.

This chapter has two sections. Firstly, we review some recent reviews on ACI and comparators, to give some general background. In this section, we provide information on most forms of ACI, and how they compare with microfracture. We do this partly because the evidence on the technologies identified in the NICE scope is limited, both in terms of number of trials and duration of follow-up. There is a problem with evidence which is not unusual with non-pharmacological therapies;

- We need long-term follow-up
- The technologies are evolving
- By the time we get long-term follow-up from a study, the technology may have been superseded.

This is unlike the situation in drug appraisals where the drug molecule does not usually change over time.

Secondly, we give an account of two recent trials of MACI®.

2.1 Systematic reviews

The characteristics and quality assessment of the reviews are reported in Appendix VI.

Inclusion criteria

Type of studies

- We looked first for systematic reviews comparing relative effectiveness of ACI (any generation) and microfracture.

Type of participants

- Adults with symptomatic articular cartilage defects.

Type of interventions

- ACI for chondral defects in the knee only. All forms of ACI were considered.

Type of comparators

- The main interest was microfracture but no restrictions were applied

Type of outcomes

The outcomes of interest, as in the NICE scope, were pain and other symptom,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 and health-related quality of life.

Searches for Systematic Reviews

Databases searched for systematic reviews published between 2004 and June 2014 were the Cochrane Database of Systematic Reviews, Medline and Embase. The websites of European Medicines Association, the US Food and Drug Administration and the CRD HTA database were also searched for Health Technology Assessments and other reports.

Detailed search strategies are outlined in Appendix II.

Study selection

Study selection was made independently by two reviewers (NW/CC/PR). Discrepancies were resolved by discussion. There was no need for discussion with a third reviewer.

We selected recent reviews that provide comparative effectiveness data for ACI versus another comparator, but some reviews on other topics such as rehabilitation were also useful.

Data extraction strategy

Data was extracted by one reviewer (CC) and checked by a second (RC) using a standardised data extraction form. Discrepancies were resolved by discussion. There was no need for discussion with a third reviewer.

Quality assessment strategy

The quality of the reviews was assessed by one reviewer (CC/RC), and checked by a second reviewer (RC/CC). Any disagreements were resolved by consensus. There was no need for discussion with a third reviewer. The following quality criteria were used for assessing systematic reviews:

- Inclusion criteria described
- Details of literature search given (and adequate
- Study selection described (and adequate)
- Data extraction described (and adequate)
- Study quality assessment described (and adequate)
- Study flow shown
- Study characteristics of individual studies described
- Quality of individual studies given
- Results of individual studies shown
- Statistical analysis appropriate

OVERALL QUALITY: high (≤1 of the criteria are not met) / medium (2-4 of the criteria are not met) / low (≥5 of the criteria are not met)

Methods of analysis/synthesis

Results were summarised narratively and in tables.

2.1.1 Results

Twelve relevant systematic reviews were included. One of these (Vasiliadis 2010A)[42] was associated with a Cochrane review (Vasiliadis 2010B)[43] but the former provides an update with more trials and is used here. The majority of reviews was rated as at least medium quality, with three reviews being rated as low quality (Goyal 2013A[44] and Goyal 2013B[45], Naveen 2012[46]), six reviews rated as medium quality (Bekkers 2009[47], Kon 2009[48], Magnussen 2008[49], Mithöfer 2009[50], Nakamura 2009[51], Negrin 2013[52]) and three reviews rated as high quality (Harris 2010[41], Vasiliadis 2010[42], Vavken 2010[53]). The quality assessment of the reviews is reported in Appendix III.

Table 30 in Appendix V shows the primary intervention studies included in the reviews. Several reviews treated separate publications from the same study, or of subgroups of a study, as separate studies. We therefore checked the original studies and in the table we have grouped all reports from each study together. The tables describing the characteristics of the reviews also record publications from the same study.

The 12 reviews included 27 papers from 19 studies. Eleven of the studies were randomised trials (RCTs), and eight were comparative cohort studies or non-randomised / quasi-randomised trials. None of the primary studies were included in all of the reviews. Of the included primary studies, one compared collagen-based ACI with periosteum-based ACI, four compared ACI with MACI, one compared open with arthroscopic ACI, three compared ACI with mosaicplasty, eight compared ACI with microfracture, and one each with bone marrow-derived mesenchymal stem cell therapy and with abrasion.

Characteristics of included reviews

Table 31 in Appendix VI shows the characteristics and quality of the included reviews. The reviews originated in various countries worldwide. None of the author teams appear to have had any specific conflicts of interest.

Objectives

Most studies sought to compare the effectiveness of ACI with that of other surgical treatments. Half of the reviews were very broad in their inclusion of comparators (Bekkers 2009[47], Harris 2010 [41], Nakamura 2009[46], Naveen 2012[46], Vasiliadis 2010[42], Vavken 2010[53]), while others were more specific, e.g. comparing different generations of ACI (Goyal 2013A[44]) or focusing on MACI (Kon 2009[48]), and comparing with microfracture (Goyal 2013B[45], Negrin 2013[52]) or osteochondral autograft transfer (Magnussen 2008[49]). One review focused on the effects of articular cartilage repair on athletic participation (Mithöfer 2009[50]).

Inclusion criteria

Study design. The reviews included various types of study designs. They ranged from studies with very broad inclusion criteria (any type of primary study (Kon 2009[48]); RCT and prospective and retrospective studies with or without a control group (Mithöfer 2009[50]); RCTs, prospective comparative studies and case series (Nakamura 2009 [51]) to studies only including level I and level II evidence / controlled trials or controlled prospective observational studies (Goyal 2013 A[44] and B[45], Harris 2010[41], Magnussen 2008[49], Negrin 2013[52]), and studies only including RCTs or quasi-RCTs (Bekkers 2009[47],Vasiliadis 2010[42], Vavken 2010[53]). Naveen 2012[46] stated that they would only include RCTs, but among the actual studies included were CCTs and comparative cohort studies. A few specified minimum follow-up times (6 months (Vavken 2010[53]), 12 months (Harris 2010[41], Magnussen 2008[49], Mithöfer 2009[50], Negrin 2013[52])) and minimum number of participants (Magnussen 2008[49]).

Participants. Inclusion criteria for participants were not given by all reviews. Some only generally referred to 'cartilage defects of the knee', in others the criteria were more specific, requiring full thickness cartilage defects of the knee (Outerbridge grades III and IV) (Harris 2010[41], Magnussen 2008[49], Mithöfer 2009[50], Negrin 2013[52], Vasiliadis 2010[42]) and in some cases also specifying anatomical location (femur, patella, trochlea) (Mithöfer 2009[50], Negrin 2013[52], Vasiliadis 2010[42]). An age range was only specified by Vasiliadis 2010[42] (15 to 55 years).

Interventions. For most reviews, the index intervention was ACI. In two reviews the focus was on MACI / newer methods of ACI (Goyal 2013A[44], Kon 2009[48]). Magnussen 2008[49] also include osteochondral autograft transfer among the index interventions. In another review the index intervention was microfracture (Goyal 2013B[45]) and the authors only reported outcomes for microfracture, so the review is listed in the tables but will not be considered in the results section. Comparators were not always explicitly stated, but included microfracture only (Goyal 2013B[45], Negrin 2013[52]), microfracture or osteochondral autograft transplantation (Bekkers 2009[47]), another ACI method (Goyal 2013A[44]), any cartilage repair technique or another generation of ACI or open

versus arthroscopic ACI (Harris 2010[41]), any other method (or placebo) (Magnussen 2008[49], Naveen 2012[46], Vasiliadis 2010[42], Vavken 2010[53]), any other method or no comparator (Kon 2009[48], Mithöfer 2009[50], Nakamura 2009[51]).

Outcomes. Often reviews did not explicitly specify outcome measures in their inclusion criteria. Whether specified or not, the focus was generally on (validated) clinical outcomes. Mithöfer 2009[50] specifically focused on outcomes related to athletic activity. Many reviews also included information on the quality of the repair tissue and on complications.

Included studies

The reviews included between three and 13 comparative studies of individual populations relevant to this review (i.e. studies not including ACI or without a comparison group were not counted), with data on total numbers of patients ranging from around 200 to over 1000 participants. Individual study populations ranged between 19 and 231 participants.

As indicated above, 11 of the 19 comparative studies included were RCTs and eight were comparative cohort studies or non-randomised / quasi-randomised trials. Follow-up was between 6.5 months and 7.5 years (most reviews included studies with at least a year's follow-up). Many of the reviews commented on the quality of the studies, which overall was generally medium to low. Reasons included small sample sizes, inadequate durations of follow-up, lack of allocation concealment, and not enough information on method of randomisation, losses to follow-up and blinding of assessment scoring. Harris (2010) reported that in their 13 included studies, quality was better in the later ones, but no studies were considered good or excellent – seven were scored as fair and six as poor. The origin of the included studies was generally not reported and only one review mentioned financial conflicts of interest of primary studies (Harris 2010[41]].

Where reported, the mean age of participants was between 26.4 and 40.4 years, between 47 and 80% were men, and mean lesion size was between 1.9 and 6.4 cm^2. Lesion sites were mainly the femoral condyles, but sites such as the patella, trochlea, and lateral tibia were also included. Both traumatic and non-traumatic lesions were included. Many of the participants had had previous surgery. Duration of symptoms before the intervention ranged between 1.5 and 10 years.

Table 1 shows the studies included in the reviews.

Table 1. Autologous chondrocyte implantation: Primary comparative studies in reviews

ACI-C vs ACI-P
RCT
Gooding 2006[21]
ACI vs MACI
RCTs
Bartlett 2005[54] MACI Verigen vs ACI-C
Zeifang 2010[55]MACI vs ACI-P
Comparative cohort
Erggelet 2010[56] MACI(Bioseed) vs ACI-P
Niemeyer 2008[57] ACI-p vs ACI-c vs MACI (but each done by a different surgeon)
Open vs arthroscopic ACI
Comparative cohort / CCT
Ferruzzi 2008[58] MACI, open vs arthroscopic
ACI vs mosaicplasty
RCT
Bentley 2003[4] ACI-P
Dozin 2005[59] ACI-P
CCT
Horas 2000[60] ACI-P (Described as RCT but inadequate randomisation method - alternation) **Horas 2003**[5] ACI-P It is not clear whether the patients in Horas 2000 are included in Horas 2003.
ACI vs microfracture
RCT
Basad 2004[7] This is presumably a preliminary report of the trial and patients reported in the first paper are expected to be included in the second report, **Basad 2010**[61] **Bachmann 2004**[62] This trial used MACI
Crawford 2012[63] MACI (Neocart)
Knutsen 2004[6] and **Knutsen 2007**[64] ACI-P
Lim 2012[65] ACI-P
Saris 2008[66]RCT ACI-P with CCI **Saris 2009**[67] **Vanlauwe 2011**[40] **Van Assche 2009**[68] (Both Van Assche references involve the same subgroup of patients from the

Saris RCT) **Van Assche 2010**[69]
Comparative cohort
Kon 2009A[70] MACI Hyalograft
Kon 2011[71] MACI Hyalograft
Minas 2009[72] Case series on effect of previous MF
ACI vs BMSC
Comparative cohort
Nejadnik 2010[73]
ACI vs abrasionplasty
RCT
Visna 2004[74] MACI fibrin glue

Gooding and colleagues compared first generation ACI-P with second generation ACI-C, and found them similar in terms of repair quality, but with ACI-P requiring more subsequent procedures.[21] They concluded that ACI-C should be used and that ACI-P should be discontinued.

One trial by Bartlett and colleagues compared ACI-C and MACI (Verigen).[54] Both gave good results but MACI appeared slightly better, though most results were not statistically significant. (There were 44 patients in one group and 47 in the other.) The advantages of MACI were reported to be no need for suturing, a shorter procedure, and a smaller incision. The proportions with good or excellent results were 72% with MAC and 59% with ACI-C.

Four studies compared ACI (mostly ACI-P) with MACI , one compared open with arthroscopic ACI, three compared ACI with mosaicplasty, eight compared ACI-P with microfracture, and one each with bone marrow-derived mesenchymal stem cell therapy and with abrasion. Clinical outcomes were measured using a wide range of different instruments. In some studies biopsies were also taken and histological outcomes reported.

Results and conclusions of reviews

The reviews generally agreed that studies were heterogeneous and had various quality limitations (as outlined above). The detailed results and the conclusions of the included reviews are in Table 32 and Table 33 in Appendix VII.

Clinical results. Improvements from clinical baseline scores were found regardless of treatment. One review suggested a small superiority of ACI (nine studies ACI-P, two ACI-C) compared to microfracture but not mosaicplasty [Harris 2010[41]], but this review did not comment on the

heterogeneity of results. Their forest plot comparing microfracture and ACI showed three studies (Basad 2004[7] and Basad 2010[61] with MACI®; Saris 2008[66] and Saris 2009[67] with ChondroCelect; Kon 2009[70], MACI with Hyalograft) with better results with ACI, and one study (Knutsen 2004 and 2007[6, 64], with ACI-P) reporting better results with MF. It was noted that the results in Knutsen showed an advantage for MF at 2 years but not at 5 years. Harris and colleagues concluded that MF showed an initial advantage which was then lost over time.[41] They also concluded that there was a trend for ACI to show better outcomes then MF, but that lack of long-term data meant that no definite verdict could be reached. Harris et al also commented on problems in interpretation due to the number of additional procedures undertaken in some studies, mainly meniscectomy and cruciate ligament repair.

Vakven et al 2010[53] compared ACI (5 ACI-P, one MACI, one fibrin glue) with mosaicplasty and microfracture, and were similarly cautious, mentioning "*a general trend for higher quality of repair tissue after ACI, suggesting better long-term results when compared to microfracture and osteochondral grafts"* especially in higher quality studies, but concluded that "*no clear recommendation can be deducted"*.

Various reviews, including Vavken 2010[53], questioned whether any small but significant differences seen in clinical outcomes were of real clinical importance. Significant differences between different generations of ACI were generally not seen. The delay in reaching maximal functional improvement (i.e. with respect to return to sports) may be slightly longer with ACI than with other interventions but overall long term durability may be greater with ACI.

Quality of repair tissue. The evidence suggested that ACI (all forms) may have a more durable repair tissue than microfracture (e.g. more hyaline-like cartilage).

Complications. Most notably, periosteum-based ACI was associated with a high rate of graft hypertrophy (over 20%) compared to only 3% with ACI-C (Harris 2011[41]). Failure rates showed a reduction over the ACI generations: ACI-P 7.7%; ACI-C 1.5%; and 0.83% in all-arthroscopic second generation ACI. Unplanned re-operation rates ranged from 27% with ACI-P to 1.4% in second generation ACI. Harris and colleagues found too few studies of third generation ACI to report failure rates.

Modifying factors. Overall, outcomes tended to be better for younger patients (<30/35 years), more active patients, patients with shorter symptom duration, and patients who had not had a previous failed surgical intervention. Results also tended to be better for smaller lesions overall, whereas ACI produced better results than microfracture in larger lesions (and its effect was largely independent of lesion size).

Recommendations for practice. Only five reviews made clear practice recommendations. Two of these (Vasiliadis 2010[42], Vavken 2010[53]) stated that the evidence was insufficient to recommend ACI over any other methods. The other three reviews agreed that microfracture was the first line treatment for smaller lesions (<1 to 2 cm^2) and that ACI was indicated for larger lesions (>2 cm^2). The opinion about mosaicplasty was divided, with one review noting that its usefulness may be limited by donor site morbidity (Harris 2010[41]).

The MSAC report[30] also reviewed previous reviews and noted that most had been inconclusive, for reasons including;

- problems with the quality of the trials and other studies
- heterogeneity of patients recruited and of ACI and MACI techniques used
- variations in ages of recruits and size of defects
- variations in previous surgery
- multiple scoring systems and lack of standard outcomes
- safety data not reported as comprehensively

2.1.2 ACI after previous microfracture

Microfracture (MF) is much less expensive than ACI, and effective in the short term in most cases. It might therefore be suggested that MF should be tried first, and ACI used when it failed.

However, there is evidence that prior MF makes ACI less effective, because of a higher failure rate. This may be related to damage to the subchondral bone. Minas and colleagues[72] compared two cohorts of patients who had ACI-P, one group (111 patients) having had previous marrow stimulation procedures (MF, drilling or abrasion arthroplasty, all based on repair of the chondral defect by development of fibrocartilage from a blood clot) and the other (214) not. The groups were similar in age, duration and size of cartilage defect, duration of follow-up, concomitant procedures such as osteotomy or ligament repair, and size of repaired areas.

Failure was defined as persistence or recurrence of symptoms, or the need for a repeat procedure, or for knee replacement. The failure rate in those who had ACI as first procedure was 8% (17/214), but was 26% (29/111) in those who had had previous marrow procedures, and 20% in those who had had MF (but numbers small 5/20).

Minas and colleagues also report a subgroup of 15 patients who had more than one chondral defect (35 defects in total) about half of which had been treated by marrow stimulation and half not, with all

then receiving ACI.[72] The failure rate was 2/18 in the previously untreated lesions and 16/17 of the previously treated ones.

If ACI is less effective after prior MF, there are implications for the interpretation of results from some of the trials. For example, the Stanmore ACI trial results were in patients who had had an average of 1.5 previous repair procedures.[75] Only 6 patients had not had a previous repair procedure so they could not compare results in those with/without previous surgery. Similarly in a case series in patients with long duration cartilage defects, those who had had previous procedures such as MF, had 29% (21/72) failure of ACI compared to a 19% (6/32) failure rate on those having primary ACI.[76] Failure was defined as requiring re-operation, somewhat stricter than in the Minas study.

One of the largest series of patients having ACI was reported by Nawaz and colleagues from Stanmore, where 1000 patients had ACI (519 with MACI, rest ACI-C and some ACI-P) from 1998 to 2008.[77] In 827 patients with full follow-up data (mean follow-up 6.2 years), graft survival was 78% at five years and 51% at 10 years. Failure of the graft was 4.7 times as likely in the 34% who had had previous procedures (microfracture, mosaicplasty and drilling – numbers of each not given).

Pestka and colleagues reported a case series wherein 28 patients had MACI after previous microfracture and a matched 28 had MACI as first procedure.[78] Failure was much commoner in the previous MF group (7/28) than in the MACI as first procedure group (1/28).

There are two implications for this review. Firstly, results seen in past trials wherein ACI was being used as a salvage procedure in patients with long-standing lesions and who had had previous procedures, may under-estimate the benefits of ACI used as first procedure in patients with chondral defects of more recent origin. Secondly, a case could be made that ACI should be used as the primary procedure.

2.1.3 Other reviews

Mithoefer and colleagues carried out a systematic review of outcomes of microfracture, including 28 studies with 3122 patients, mean follow-up 41 months, with 1524 patients having follow-up of > 5 years.[79] They noted good results in short-term functioning, but with need for further surgery increasing after 2 years, with rates of up to 31% by 5 years. Only 5 studies provided data beyond 5 years, of which one was an RCT and four were case series. At 6-7 years, most (67% to 86%) patients had improved knee functioning compared to baseline.

Several reviews examined factors that might predict success or failure. Behery and colleagues[80] reviewed 12 case series with 270 knees and found that none of age, gender, duration of symptoms and lesion size significantly predicted outcomes. They noted successful use of ACI in patients over age 50 in three studies. They concluded that the lack of association with lesion size made ACI preferable to microfracture in larger lesions. Another review from the same group[81] looked at factors which might influence the choice of repair method, and concluded that microfracture was less effective in larger lesions, when larger was defined (in different studies) as being greater than $2cm^2$ to $4cm^2$.

Chalmers and colleagues set out to systematically review activity-based outcomes (Tegner, Lysholm, KOOS, IKDC and the physical activity component of SF-36) after MF, ACI and mosaicplasty.[82] They found only five studies that reported return to sporting activity. Return was faster after microfracture than ACI, but beyond two years, activity scores deteriorated after MF but remained stable after ACI, though there was variation amongst sports. They noted the lack of long-term data on effects on later osteoarthritis.

2.1.4 Mosaicplasty

Early results from the Stanmore trial (Bentley et al[4]) showed good or excellent results in 88% after ACI-P or ACI-C compared to 69% after mosaicplasty, and the results at a minimum of 10 years follow-up showed that repairs failed in 55% (23/42) of the mosaicplasty group and 17% (10/58) in the ACI group. For ACI, the patients in this trial were a difficult group, having a mean duration of symptoms of 7.2 years and an average of 1.5 previous procedures (excluding arthroscopy).
The Stanmore trial was omitted from the review by Harris et al 2010[41] which only had two studies of mosaicplasty, both favouring ACI but with very wide confidence limits which overlapped with no difference.

The review by Vasiliadis et al[42] identified three trials of mosaicplasty against ACI, two against ACI-P and one (Bentley[4]) with both ACI-P and ACI-C. They reported that one trial (Horas 2003[5]) favoured mosaicplasty but another (Dozin 2005[59]) found no difference.

Vavken et al, reviewing the same studies reported that the Horas trial showed no difference in clinical scores.[53]

Bekkers and colleagues concluded that single plug mosaicplasty was the best option for small (less than 1 cm^2 osteochondral lesions).[47]

The Medical Services Advisory Committee concluded that mosaicplasty should probably not be a comparator to MACI on the grounds of very low use in Australia.[30]

2.2 Trials

2.2.1 Methods

Inclusion and exclusion criteria

Inclusion criteria

Type of studies

- Randomised controlled trials (RCTs) comparing second and third generation ACI and following patients for at least two years.
- Observational studies with at least 50 participants and follow-up of over three years were also considered, for results in routine care, adverse events, and costs.

Type of participants

- Adults with a symptomatic cartilage defect (chondral defect) but without advanced osteoarthritis were included. The chondral defects can be on the femur, tibia or patella
- The NICE scope did not report age restriction however, we included studies comparing interventions of interest in patients aged 18 years and over.

Type of interventions

- ACI for chondral defects in the knee only. (ACI has also been used in shoulder, elbow, ankle and hip problems.) The forms of ACI considered were
    - The ChondroCelect ACI, referred to by TiGenix as characterised chondrocyte implantation (CCI).
    - The Matrix ACI system (MACI®) from Sanofi.
    - "Traditional ACI" the term used by NICE to describe ACI provided in the UK by hospitals that using cells produced by non-commercial units, for their own use or for use in trials.

Type of comparators

- Microfracture is the main comparator. Mosaicplasty is now in limited use, for small defects only. Osteochondral grafts from cadavers can be used but are not to any significant volume in the UK and were not considered.

Type of outcomes

The outcomes considered, as also mentioned in the NICE scope, were as follows

- pain
- 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.

Box 6 summarises some of the outcomes used in ACI studies

Box 6. Outcomes used in cartilage repair studies.

The Lysholm score	Range of 0 to 100 (best), based on patient responses on 8 aspects: pain, limping, locking, stair-climbing, need for supports, instability, swelling and squatting.
The Tegner score	A level of activity measure from best 10, with ability to take part in competitive sports at a very high level, to worst 0, disabled.
The Knee Injury and Osteoarthritis Outcome Score (KOOS)	Assesses pain, symptoms, activities of daily living, sport and recreational activities, and knee-related quality of life, with scores of 0 (worst) to 100 (best).
Cincinnati knee score	Based on symptoms (pain, swelling) and function (walking, climbing stairs, running) with a score of 0 (worst) to 10. Variants include a sports rating from 0 to 100 points.
The International Cartilage Repair Society (ICRS)	This assesses quality of tissue repair rather than patient reported outcomes. It could be argued that the quality of tissue repair might be useful for extrapolating from short-term histological results to long-term osteoarthritis and need for knee replacement, but there is far from perfect correlation between symptoms and the degree of OA.
International Knee Documentation Committee (IKDC)	Range 0 (worst) to 100 (best), based on function, symptoms, and range of motion. The version “IKDC Subjective” is so-called because it is completed by patients.

Howard and colleagues carried out a high quality systematic review to compare the various patient reported outcome measures used in assessing the effects of ACI.[83] They included 42 studies, grading quality of studies with the Coleman Methodology Score. They concluded that the Lysholm and IKDC were the most responsive to change (i.e. showing larger effect sizes), but that IKDC and KOOS-Sports might reflect long-term outcomes better. They noted that the Cincinnati knee score also appeared satisfactory but based on few studies that there were several versions of this score, and many studies were excluded because the authors failed to state which version was used.

Exclusion criteria

- We did not include trials of ACI-P in this section on the grounds that it had been replaced by third generation ACI, but it should be noted that most long-term outcomes are from studies of 1st generation ACI.

Search strategy

The databases searched for primary studies on clinical effectiveness published between 2010 and June 2014 were the Cochrane Central Register of Controlled Trials, Medline, Embase and the Web of Science.

Also the inclusion lists of recent systematic reviews were checked and additional searches were done for ongoing or recently completed studies.

Auto-alerts in Medline and Embase were run for the duration of the review to ensure that newly published studies were identified.

Detailed search strategies are outlined in Appendix II

Identification of studies

Two independent reviewers (NW/PR) screened titles and abstract of the results retrieved against the inclusion criteria. Those studies meeting the inclusion criteria were retrieved in full and checked for final inclusion by two reviewers (NW/PR) independently. There was no need for discussions with a third reviewer.

Data extraction strategy

The data extraction template used by Harris and colleagues was used and adapted for this review.[29] One reviewer (DS/RC) extracted data which was checked by a second reviewer (RC/DS).

Quality assessment strategy

The quality of the studies was assessed using the modified Coleman methodology score.[29] There are 15 items in total namely inclusion criteria, power, alpha error, sample size, randomization, follow-up, patient analysis, blinding, similarity in treatment, treatment description, group comparability, outcome assessment, description of rehabilitation protocol, clinical effect measurement and number of patients to treat. A study could be rated as 'excellent' if the total score is between 85 and 100, rated as 'good' for scores between 70 and 84, rated as 'fair' with scores between 55 and 69 and finally categorised as 'poor' for scores of <55.

The quality of the study was assessed by one reviewer (DS/RC) and checked by a second reviewer (RC/DS).

2.2.2 Results

A total of 1672 records were retrieved by the searches. The title and abstracts were screened for inclusion and exclusion. Based on titles and abstracts, 104 records were considered possible inclusions and full texts of these were obtained. Out of 104 articles, two RCTs were included as definite inclusions and the remaining 102 articles (which included the 12 systematic reviews included above) were excluded. The reasons for exclusion of 26 studies retained for final discussion by both reviewers is given in Table 2. (One of the excluded studies, reported in Saris 2008[66] and 2009[67] and Vanlauwe 2011[40], is described in the next chapter.)

Table 2. Reason for exclusion of studies

First author and year	Reason for exclusion
Bartlett 2005 [84]	Technique includes bone graft
Bartlett 2005 [54]	ACI (1st generation) v MACI. 1 year follow up
Bentley 2003 [4]	ACI (1st generation)
Bentley 2012 [75]	ACI (1st generation)
Benthien 2011 [85]	Not a systematic review – no details of individual studies are given
Cole 2011 [86]	Not a form of ACI we are including (Cartilage Autograft Implantation System (CAIS))
Crawford 2012 [63]	Not a form of ACI we are including (NeoCart)
Dozin 2005 [59]	ACI-P
Ebert 2010 [87]	Comparing rehabilitation approaches after MACI
Ebert 2012 [88]	Comparing rehabilitation approaches after

	MACI
Edwards 2013 [89]	Comparing rehabilitation approaches after MACI
Harris 2010 [90]	Only includes one RCT that is not on ACI
Knutsen 2004 [6]	Old RCT of ACI-P
Knutsen 2007 [64]	5-year results from above trial. ACI-P
Lim 2012 [65]	ACI-P
Panseri 2012 [91]	Osteochondral defects.
Rodriguez-Merchant 2012 [92]	Short narrative review
Ruano-Ravina 2006 [93]	Too old
Saris 2008 and 2009 [66, 67]	ACI-P
Trinh 2013 [94]	About osteotomies not ACI
Toonstra 2013 [95]	Case series, only 20 patients, no controls.
United Healthcare 2013 [96]	Not based on a systematic review.
Van Assche 2010 [69]	ACI-P
Van Assche 2009 [68]	ACI-P
Ziefang 2009 [55]	ACI-P vs MACI and small numbers.

MACI® versus MF

Two studies, Basad et al 2010[61]; Saris et al 2014[97], compared MACI® against MF in patients with a symptomatic cartilage defect in the knee.

Basad et al 2010

This RCT compared MACI®, a third generation ACI (then a Genzyme product) against MF in patients with symptomatic cartilage defects. Patients in the trial came from one centre (the principal author's clinic in Germany) between 2000 and 2005.

Quality assessment

Using the modified Coleman methodology score, the study scored a total of 45 suggesting that the quality of the study is poor, though this is partly due to failure to report items, so the study scored '0' points for those items. The enrolment rate was not reported, losing a maximum of 9 points. The power of the study (maximum score of 6) was not reported and it was not clear whether blinding of outcomes assessment (maximum score of 6) was done. There was no information available on effect size (maximum 6), relative risk reduction (maximum 6) and absolute risk reduction (maximum 6). There were some baseline differences between the two groups, so the study scored 6 out of a possible

9. The study also lost points on the number of patients retained at the end of follow-up – 86.4% completed the two year follow-up period thereby scoring 4 points instead of a maximum 6.

Patient characteristics

Basad and colleagues included 60 patients aged ≥18 and ≤50 years with a single symptomatic chondral lesion of femur or patella of size between 4 and 10 cm^2; 40 received MACI® and 20 MF. The mean ages of patients in the MACI® group were 33 years and 37.5 years in the MF group. The mean BMI of patients in the MACI® was slightly lower compared to those in the MF group (25.3 vs. 27.3 kg/m^2). Previous surgery, if any, was not reported. Most defects in both groups were condylar (73% in MACI® and 80% in MF), with the remaining lesions being in patellar-trochlear region (28% in MACI and 20% in MF). Most patients were male (63% in MACI and 85% in MF). Patients in the MACI group had had symptoms for 2.2 years and those in the MF group for 2.5 years.

Details of intervention and comparators

Patients in the intervention group received MACI®. The published paper states that the original protocol of the study had three interventions including two MACI groups and one MF group. In the two MACI groups, two different collagen matrices (supplied from two different manufacturing sites – name not reported) were used. The two matrices were considered identical in all aspects so the two MACI groups were combined in the analysis.

Arthroscopy was done in all patients to assess their eligibility for the study (mainly isolated defect >4 cm^2). Patients in the MACI group had a sample from healthy cartilage sent for cell culture. Patients allocated to the MF group received treatment in one procedure. The MACI group returned four to six weeks later to have the chondrocyte seeded collagen scaffold implanted into the defect, cell side down facing the subchondral bone, sealed with a thin layer of fibrin sealant.

Patients in both groups could also receive treatment for other concomitant lesions of cartilage or meniscus. All patients underwent a post-surgery rehabilitation programme. Those in the MF group received the rehabilitation programme recommended by Steadman and colleagues which included 6 weeks of partial weight bearing with 10 kg weight on crutches, continuous passive motion and physiotherapy. After six weeks, patients were allowed to gradually progress into full weight-bearing. The rehabilitation programme in the MACI group was slightly different. All patients had a plaster cast for 2 days after surgery in order to prevent graft delamination. Then, for the next 8 weeks, the programme included continuous passive motion, physiotherapy and partial weight-bearing with 10 kg weight on crutches.

All patients also received low-molecular heparin each day during the partial weight bearing phase to prevent deep vein thrombosis.

Duration of follow-up

Patients were followed up for two years.

Outcomes:

The primary outcome measures included the Tegner, Lysholm and ICRS scores. The Tegner score is related to activity levels of an individual, whereas the Lysholm score is related to pain, stability, gait and clinical symptoms. The primary outcomes were measured at 8 to 12 weeks, 22 to 26 weeks and 50-54 weeks after surgery. One week after surgery, MRI scans were done in patients to see if there was delamination and graft hypertrophy. The efficacy population was defined as patients completing at least six months of follow-up while completers were defined as those completing two years of follow-up. The definition of failure was not given.

Results

56 patients (39 in MACI and 17 in MF) completed at least six months of follow-up period and 48 patients (33 in MACI and 15 in MF) completed two years of follow-up. There was one early failure in the MF group but time was not reported. Two patients in the MF group (one pregnancy, and one who had mosaicplasty) and one patient in the MACI group dropped out of the study

There was improvement in the mean Lysholm score in both groups at year 1. The improvement in the MACI group persisted up to year 2 (52 at baseline, 95 at 12 months, 92 at 24 months) but it declined in the MF group after 12 months (55 at baseline, 81 at 12 months, 69 at 24 months). The improvement in Lysholm score from baseline to follow-up was statistically significant in both groups ($p<0.0001$).

The improvement in the median Tegner score from baseline was greater in the MACI group than in the MF group. The Tegner score in the MACI group improved from level 2 to level 4 at 12 months, and remained at the same level at 24 months. The Tegner score in the MF group improved from level 2 to level 3 at 12 months, which was maintained at 24 months. The improvement from baseline to end of follow-up was statistically significant in both groups ($p<0.0001$) but the improvement was statistically significantly greater in the MACI group than in the MF ($p=0.04$).

None of the patients had treatment-related adverse events (TEAEs). Some patients had issues with irritation during increased weight-bearing, treated with non-steroidal anti-inflammatory drugs (NSAIDs) and by returning to partial weight-bearing for a week. In the MACI group, one patient had persistent pain after 12 months and had arthroscopy at which even and firmly regenerated cartilage repair was seen. The patient had persistent subchondral oedema. To relieve oedema, bone grafting was done.

Comments

The Basad group has had long experience with ACI so their results may be better than might be seen in routine care. Patients were treated with fairly short duration of symptoms, which may improve outcomes after ACI.

Saris et al 2014 (SUMMIT trial)

This was a prospective, open-label, parallel-group, multicentre (16 European sites), RCT comparing Genzyme MACI® against MF.

Quality assessment

Using the modified Coleman methodology score, the study scored a total of 72 suggesting that the quality of the study is good. Information on blinding of outcomes assessment was not fully reported. There was no information on effect size, relative risk reduction and absolute risk reduction.

Patient characteristics

Patients aged between 18 and 55 years with one or more symptomatic cartilage defects, Outerbridge grade III or IV focal defects of size ≥3 cm^2 on medial or lateral femoral condyle and/or trochlea and with a moderate to severe Knee Injury and Osteoarthritis Outcome Score (KOOS). There were 72 patients in each group. Most patients were male (62% in MACI, 67% in MF). Patients in the MACI group were slightly older than in the MF group (35 vs. 33 years). Mean BMIs were similar (26 kg/m^2). 90% of patients in the MACI and almost 84% in the MF had undergone previous knee surgery. The most common prior procedures included diagnostic arthroscopy (50.3%), marrow stimulation techniques (in MACI group, microfracture 19%, drilling 11%), debridement of the lesion (26.3%) and loose body removal (23.2%). Patients in the MACI group had had knee symptoms for longer than those in the MF group (mean of 5.8 years, range 0.05 to 28 years, vs. mean 3.7, range 0.1 to 15.4 years). The mean defect size of the lesions was similar across the group (4.9 cm^2 in MACI and 4.7cm^2 in MF). Most defects in both group were on the medial femoral condyle (75% in MACI, 74% in MF) followed by the lateral femoral condyle (18% in MACI, 21% in MF) and trochlea (7% in MACI, 6% in MF). No tibial defects were reported.

Details of intervention and comparators

All patients underwent arthroscopy at baseline to examine their cartilage lesion and surrounding tissues. A small biopsy of cartilage (~ 200 mg) was taken from a non-weight bearing healthy area of the femoral condyle in all patients before randomisation, done using an interactive voice response system and computer-generated randomization system. Those randomised to MF had it immediately. The technique recommended by Steadman and colleagues was followed, which included debridement

and drilling multiple holes of centres 3-4 mm apart and 4 mm deep in the subchondral bone. Biopsies from patients receiving MF were preserved in case they later require MACI treatment. The MACI group had implantation of the cells 4 to 8 weeks after biopsy, by mini-arthrotomy. The MACI implant was trimmed to the size of the cartilage defect and implanted securely using a thin layer of fibrin sealant.

After surgery, both groups underwent the same rehabilitation programme but individualised for patients. This was a 4 phase programme recommended by Steadman and colleagues.[98]

Duration of follow-up

Patients were followed up for two years. At the end of the follow-up, arthroscopy was performed to assess the condition of the knee.

Outcomes

The primary outcome measures were changes in KOOS pain score and function (sports and recreational activities subscore) from baseline to year 2. Other outcome measures included histological evaluation of structural repair biopsy specimens, as measured by the microscopic ICRS II Overall assessment; MRI assessment of the degree of defect fill, as measured by the scale of the Whole Organ MRI Score (WORMS: 0% to 25%, 26% to 50%, 51% to 75%, 76% to 100%)

In the study, a responder was defined as '*having at least a 10-point improvement in both the KOOS pain and function subscales, whereas anyone not meeting both criteria was regarded as a nonresponder'*.

Failure was defined as '*at any time after week 24, ….. a patient and physician global assessment result that was the same or worse than at baseline, a <10% improvement in the KOOS pain subscale, physician-diagnosed failure ruling out all potential causes, and the physician deciding that surgical retreatment was needed'*. Those diagnosed as failures by physicians were further assessed by an independent treatment failure evaluation committee, who decided whether those cases were failures.

Adverse events were defined as '*any undesirable physical, psychological, or behavioural effect experienced by a patient, independent of treatment relatedness'*. The definitions given in the Medical Dictionary for Regulatory Activities were used to categorise severity of adverse events.

Results

144 patients were included in the study, 72 in each group. 95% (137/144) patients completed the two year follow-up period. None of the patients in the MACI® group discontinued treatment due to lack of efficacy whereas three patients in the MF group discontinued study because of lack of efficacy.

The mean change in KOOS pain score from baseline to two years was significantly greater in the MACI group than in the MF group (45.5 vs. 35.5, difference between groups 11.76, p=0.001). The change in the KOOS function score from baseline to two years was also significantly greater in the MACI group (46 vs. 36.1, difference between groups 11.41, p<0.001). Saris et al (2014) reported that the improvement in the KOOS pain and pain score in the MACI over MF was observed at 36 weeks and maintained throughout the study period.

The proportion of responders was significantly greater in the MACI group than in the MF group (87.5% vs. 68.1%, p=0.016) with more non-responders in the MF group (31.9% vs. 12.5%). Subgroup analyses found that more patients responded after MACI than after MF if patients had the following characteristics: male with a median age of <34.5 years, only one lesion, lesions results as a result of acute trauma, history of one previous surgery, symptoms for >3 years (symptomatic response in those with under 3 years duration 82% with MACI and 69% with MF; over 3 years 92% and 67%) and if size of lesions were >4 cm^2 and located on the medial femoral condyle. However, there were no statistically significant differences in response rates whether patients had or had not had previous cartilage surgery.

Table 3. Response rates after prior cartilage procedures

	MACI®	**MF**
Prior cartilage surgery		
No surgery	90%	74.2%
1 previous repair	87%	67.9%
>1 previous repair	84.2%	53.9%

In patients with larger lesions, ACI was reported to be more successful, 97% responders for MACI versus 77% for MF.

The improvements in other domains (activities of daily living, knee-related quality of life, other symptoms) of the KOOS subscales were also statistically significantly greater with the MACI than with the MF. The mean differences between the two groups were;

- for the domain, activities of daily living, difference 12.01 (mean change of 43.7 with MACI from baseline to two years; 33.2 with MF) at two years, estimated mean difference 12.01, p<0.001
- for knee-related quality of life (mean change of 37.4 from baseline with MACI from baseline, 30.l with MF), estimated mean difference 8.98, p=0.029
- for other symptoms (mean change of 35.4 with MACI from baseline, 27.8 with MF), estimated mean difference 11.61, p<0.001

At two years follow-up, the modified Cincinnati Knee score was significantly greater with MACI than with MF (1.05, p=0.002). The International Knee Documentation Committee (IKDC) score also showed favourable results for MACI (mean change from baseline with MACI 32.8 vs. MF 29.5), however, the difference between the two was not statistically significant (p=0.069).

Comparison of treatment failure rates between treatment groups was not conducted because of the small number of failures - only two patients in the MFX and none in the MACI group.

At two years follow-up, 116 patients (60 in MACI, 56 in MF) underwent second-look arthroscopy and biopsy. There was good structural tissue repair with both treatments, and the repair was similar to the surrounding healthy cartilage. The mean ICRS II overall assessment scores of the two treatments were similar (63.8 with MACI, 62.3 with MF, difference of 1.52, p=0.717). The proportion of patients with overall assessment scores of normal or nearly normal (grade I/II) was greater in the MACI group than in the MF group (76% vs. 60%).

134 and 139 patients underwent MRI evaluation at year 1 and year 2 respectively. At year 1, the improvement was similar but at year 2, more patients in the MACI group had a defect fill of >50% of the defect depth than those in the MF group (83% vs. 77%).

More patients in the MF group complained of treatment related adverse events than in the MACI group (83.3% vs. 76.4%), the intensities of which were mild to moderate. The most commonly reported AE was arthralgia (57.6% overall - 51.4% MACI, 63.9% MF). Other events included back pain (11.1% MACI, 9.7% MF), joint swelling (9.7% MACI, 5.6% MF), joint effusion (6.9% MACI, 5.6% MF), pyrexia (5.6% MACI, 2.8% MF), cartilage injury (4.2% MACI, 12.5% MF), procedural pain (4.2% MACI, 5.6% MF), ligament sprain (2.8% MACI, 5.6% MF). One patient (1.4%) in each group discontinued treatment due to AEs. More patients in the MF group had serious AEs than in the MACI group (26.4% vs. 15.3%) such as treatment failure, cartilage injury and arthralgia.

Similar proportions of patients in the two groups underwent at least one subsequent surgical procedure (8.3% in MACI and 9.7% in MF). Two patients in the MACI group and none in the MF group underwent two subsequent surgical procedures. It has been reported that increasing age (not clear at what age) significantly decreased the likelihood of undergoing further procedures (p=0.038).

Comments

Two factors will have reduced the chance of improvement – the long duration of symptoms before ACI (5.8 years), and the high proportion (37%) that had had previous surgery (not counting arthroscopy).

2.3 Summary of EMA EPAR report

The EMA made a positive recommendation on MACI® (manufactured by Genzyme Europe but then owned by Sanofi) on 25th of April 2013. MACI® has been recommended for the '*repair of symptomatic, full-thickness cartilage defects of the knee of 3-20 cm^2 in skeletally matured adult patients'*.[39] The product is available as an implantation matrix consisting of cultured chondrocyte cells on a membrane (500,000 to 1 million cells per cm^2).

The clinical evidence on MACI® came from the SUMMIT trial[97] (described above) which reported that MACI® was better than MF in treating symptomatic cartilage defects of the knee with size of the lesions ranging between 3 and 20 cm^2.

The EMA made a positive recommendation on ChondroCelect (TiGenix) on 25 June 2009.[37] ChondroCelect was recommended for the '*treatment of repair of single symptomatic cartilage defects of the femoral condyle of the knee (International Cartilage repair Society [ICRS] grade III or IV) in adults.'*

The clinical evidence on ChondroCelect came from study TIG/ACT/01/2000 (described in detail in Chapter 4 – Vanlauwe et al 2011[40]), a phase III, randomised, multicentre trial comparing ChondroCelect against MF in patients with a single symptomatic cartilage lesions of the femoral condyles of the knee. At the time of appraisal, results from 12, 18 and 36 months were available but we now have the five year results from Vanlauwe et al 2011.[40]

Discussion and conclusions on clinical effectiveness: see end of Chapter 4.

3 Chapter 3 - Systematic review of existing economic studies for ACI

3.1 Introduction

The objective of this chapter was to conduct a systematic review of existing economic evaluations (including any model-based economic evaluations) of the use of autologous chondrocyte implantation, microfracture and mosaicplasty for repairing symptomatic articular cartilage defects of the knee. We searched the literature since the last HTA review[3] for economic evaluations including any existing models, to help inform our economic modelling.

3.2 Methods

The systematic search used: Medline OVID (2004 to 6 July 2014), Embase OVID (2004 to 6 July 2014), NHS Economic Evaluation Database (issue 2 of 4, April 2014) and the Web of Science Core Collection (2004 to 6 July 2014). Weekly auto-alerts were set-up in OVID Medline and Embase for any new studies added to the database subsequent to July 2014. The search terms included economic and quality of life (QoL) terms cross referenced with chondrocyte implantation terms. The search was limited to studies published since the searches were done for the last HTA review[3]; that is, from the year 2004. The search was also limited to studies published in English Language and Humans. Details of the search strategies are provided in Appendix VIII.

Two reviewers (HM and PR) independently reviewed titles and abstracts to identify potentially relevant papers. Consensus was achieved by discussion, but where consensus was not agreed, a third reviewer (NW) reviewed the abstracts to reach agreement. Abstracts were considered relevant to this review if they were a full economic analysis (including any economic models) on the use of autologous chondrocyte implantation, microfracture and mosaicplasty for repairing symptomatic articular cartilage defects of the knee. Abstracts which provide useful information for the economic model (such as costs, utilities and transition probabilities) were retained but not included in this review.

We obtained the full-text articles of potentially relevant abstracts. The reference lists of retrieved articles were checked for potentially relevant papers that met the inclusion criteria. A data extraction

form was developed to capture the main characteristics and economic factors. We critically appraised full economic evaluations against the framework for quality assessment of economic evaluation studies developed by the consolidated health economic evaluation reporting standards (CHEERS) group.[99] If the studies contained an economic model, they were further assessed against a framework for the quality assessment of decision analytic modelling adapted from Philips et al.[100]

3.3 Results

The searches identified 272 potentially relevant citations published since 2004. After reviewing the abstracts, 4 studies remained including the HTA review by Clar et al [3](2005) [Derrett et al, 2005[101]; Gerlier et al, 2010[102]; Samuelson et al, 2012[103]]. A further two articles were identified from the clinical effectiveness searches [MSAC, 2010[30]; Koerber et al, 2013[104]]. In total, six articles were retained for data extraction. Figure 1 depicts a flow diagram of the abstracts identified and number of studies included.

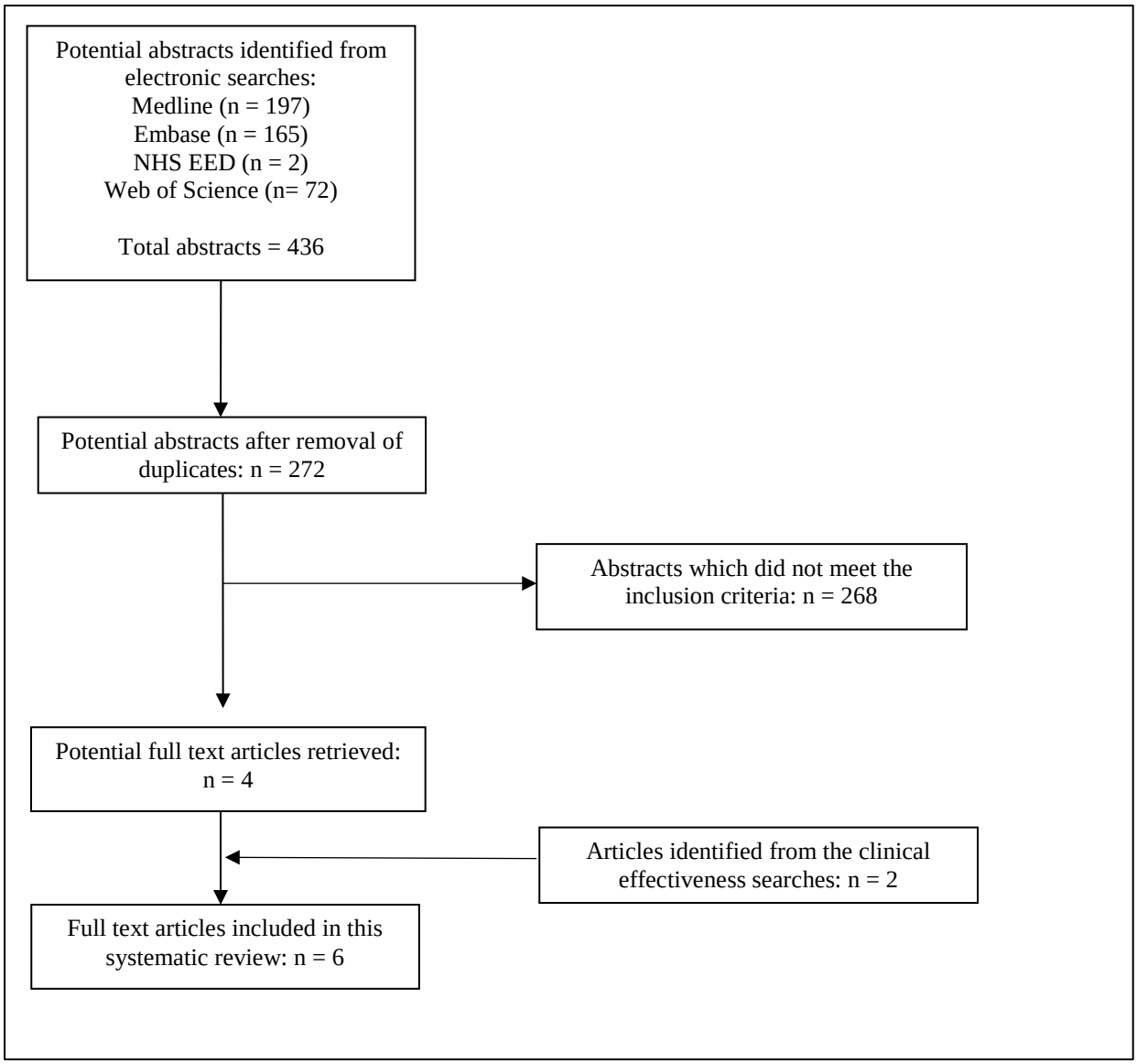


Figure 1. PRISMA flow diagram for cost-effectiveness studies

Of the six publications, two of the publications have been summarised (see below). The Clar et al[3] study is based on previous work by some of the authors of the current report and the MSAC report published in 2010[30] only compared the costs as the Committee assumed that the clinical effectiveness for the different interventions were identical.

The HTA review by Clar and colleagues[3] compared ACI with microfracture and mosaicplasty and the authors attempted to calculate reliable costs per QALY; however, they felt this was not possible due to the absence of data which was required. For example, quality of life data was limited to around 2 years; and no long-term studies (i.e. 20-30 years) were available on the incidence of osteoarthritis and the need for total knee replacement (TKR). The short-term modelling (quality of life improvements at 2 years) found that the gain from ACI versus microfracture would have to be between 70-100%

greater over two years for the cost per QALY for ACI compared with MF to be within the £20-30k threshold. For the medium-term modelling (using 10 year success rates), the authors found that if the quality of life gains were to be maintained for the next 10 years, than for ACI relative to microfracture the quality of life gain would only have to be between 10-20% greater to justify the additional cost of the intervention and to be cost-effective within the £20-30k threshold. For the longer-term modelling there may be a need to offer some (or all) patients TKR, so a 50 year time horizon was considered appropriate. The authors found that for this scenario mosaicplasty was dominated, and moving from microfracture to ACI was associated with an ICER between £3,500 to £5,500 (cells were assumed to cost only £3,200). Overall, the authors concluded that there was insufficient evidence at the moment to say that ACI was cost-effective compared with microfracture or mosaicplasty.

The MSAC report published in 2010[30] compared the costs of MACI/ACI with mosaicplasty and microfracture in patients aged between 15 and 55 years suffering from a focal defect in an otherwise normal knee. In the absence of conclusive effectiveness data, the Committee assumed that the clinical effectiveness for all the different interventions were identical and a cost-minimisation analysis was conducted. Resource use was determined by an Advisory Panel and the costs of the different procedures were obtained from various sources, e.g. the cost of autologous chondrocyte transplantation was obtained from the prosthesis price list. The authors assumed that assessment costs and rehabilitation costs were identical so were not included in the comparison. The price year (and time horizon) was not explicitly stated for the different resource use items, except for the prostheses (August 2010). The cost analysis found that the total costs of MACI/ACI (biopsy and grafting) procedure were significantly higher per knee than either mosaicplasty and microfracture ($14,083 vs. $2,639 and $1,405, respectively). The main cost difference between the procedures was that MACI/ACI required the cost of the chondrocyte cell culture and Tisseel sealant ($11,780). The Committee felt that the conclusions which can be drawn from this review were limited by the quantity and the quality of evidence.

The updated MSAC report published in 2012[30] concluded that MACI was superior to microfracture (and mosaicplasty) with respect to less need for subsequent surgery and also in terms of clinical outcomes; therefore a costing analysis was no longer sufficient and a cost-effectiveness/cost-utility analysis was required. A proposed model structure for the economic evaluation was presented using a decision tree with a Markov process, along with information on resource use and costs. They stated utility values would be obtained from the literature. However, no results of the cost-effectiveness analysis were presented.

Of the remaining four published peer-reviewed journal articles which are summarised in Table 1: one study was a cross-sectional retrospective study (Derrett et al[101]) and the other three studies were

decision analytical modelling studies (Gerlier et al[102]; Samuelson et al[103]; Koerber et al[104]). The retrospective study was conducted in the UK, and the other three studies were based on literature and some trial data from Belgium, Germany and the USA. Three studies assessed the cost-effectiveness of ACI compared with other interventions: mosaicplasty (Derrett et al [101]); microfracture (Gerlier et al [102]); mosaicplasty and microfracture with different versions of ACI (ACI-C, ACI-P and MACI) (Koerber et al[104]); Samuelson et al[103] compared ACI-C with ACI-P to see whether it was more cost-effective.

The patient populations varied. The retrospective study by Derrett et al[101] was based on 95 patients, of whom 53 patients received ACI, 20 patients received mosaicplasty and 22 patients were on the waiting list for ACI. The patients who received ACI were slightly younger than those who had received mosaicplasty (31.9 years vs. 34.9 years; p = 0.17) and more men received ACI (53% men vs. 47% women) compared with mosaicplasty (45% men vs. 55% women). The three economic models were based on clinical data and data from the literature. Gerlier et al[102] compared adult patients who were less than 50 years of age (a mean age of 35 years at model entry) with symptomatic cartilage lesions of the femoral condyles who had not yet developed osteoarthritis and the key efficacy data came from the TIG/ACI trial.
Samuelson et al [103] compared adult patients with a mean age of 30 years with a focal chondral injury which satisfied the conditions for an ACI repair.
The model by Koerber et al[104] was said to be based on the model by Gerlier et al[102]. In their supplementary file they stated that the study population was patients aged 32 years with symptomatic, isolated cartilage defects and no contra indication. None of the economic models specified the number of hypothetical patients used for the modelling.

The time horizon for any study should be long enough to capture all the benefits that would accrue from the different interventions. The follow-up length in the studies varied. The Derrett et al[101] study was based on follow-up data for two years. The economic model by Gerlier et al[102] used two time horizons: a short-term time horizon of 5 years to take into account knee pain and mobility after the initial intervention (this information was obtained from a 5 year RCT which compared ACI with ChondroCelect (CC) and microfracture) and a long-term 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. Samuelson et al[103] based their model on 10-year time horizon which corresponded with the longest term evidence which was available in the literature. Koerber et al[104] stated that on the basis of the German life expectancy of the patients in the model the timeframe was set to 47 years. Although the authors did not explicitly state the cycle length – from the information provided this can be deduced as one year. Both Gerlier et al[102] and Samuelson et al[103] did not report the cycle length which

was used in the model and none of the three studies applied a half-cycle correction to the economic models.

Study perspective is crucial to the economic evaluation as it will determine whether the appropriate resource use and costs have been collected, calculated and reported. Only two studies explicitly stated the viewpoint for the economic analysis: Gerlier et al[102] conducted the study from the perspective of the global healthcare payer; whereas Koerber et al[104] conducted their study from the viewpoint of the German statutory health insurance. All four studies conducted a cost-utility analysis where the final outcomes were reported as quality-adjusted life years (QALYs). In addition, the study by Derrett et al[101] used a range of outcome measures to compare the groups after surgery. The post-operative group consisted of patients who received either ACI or mosaicplasty who were compared with the ACI waiting list group. Outcome measures these included:

- the Cincinnati knee rating scale which assesses 11 components including subjective symptoms such as pain and swelling and functional activity level such as walking and climbing stairs scores – these scores were higher in the combined surgery group than the waiting list group;
- the Pain Disability Index which helps patients measure the degree their daily lives are disrupted by pain - the authors found that patients in the combined surgery group had less pain than the waiting list group (p=0.09); and
- the generic health-related quality of life - EQ-5D-3L measure. Patients in the combined group had statistically significantly higher EQ-5D scores than the waiting list group (0.61 vs. 0.41; p=0.03). The EQ-5D measure was used to calculate the quality-adjusted life years.

The study by Gerlier et al[102] used data from the SF-36 measure to calculate QALYs (this information was collected over a period of 60 months after randomisation from an RCT); in addition they also used the Knee injury and Osteoarthritis Outcome Score (KOOS) which evaluates 5 key dimensions – pain, symptoms, activities of daily living, sport and recreation function and knee-related quality of life. Samuelson et al[103] obtained utility values from the literature to calculate QALYs, although they did not specifically state which instrument or what method was used to estimate these utility values which were used in the model. In addition, some studies used in the model had used the Lysholm knee score (this measure contains eight domains with a higher score indicating a better outcome) to estimate the utility values. Koerber et al[104] obtained from the literature (no information sources were provided) and were based on the following: utility after treatment pain free (high functionality), utility with low functionality of the knee (medium functionality) and utility before knee prosthesis with strong pain (low functionality) [Koerber et al[104]].

Derrett et al[101] provided a comprehensive breakdown of resource use and costs which were collected for the economic evaluation. These included secondary-care resource use related to each procedure which was collected from patients' electronic and medical records from the time-point of the first pre-operative outpatient appointment to 2 years post-operatively. In addition, they also stated price year for which the costing was undertaken (year 2003-2004). The resource use and costs of the surgical procedures and the follow-up costs after initial interventions which were used in the model have been comprehensively listed by Gerlier et al[102] This included information detailing the length of stay for each procedure and follow-up stage and also stating the price year for the economic analysis (year 2008). Both Samuelson et al[103] and Koerber et al[104] provided resource use and cost information, however it was not as detailed as the two earlier studies. For example, for the different procedures the components were not individually listed and the price years for which the economic analysis was not explicitly stated – therefore researchers cannot use these unit costs for their own studies or to conduct a cost comparison with their own or with other studies.

All three economic models performed discounting using both 3% for costs and outcomes, except for Gerlier et al[102] who used 1.5% for outcomes. Derrett and colleagues[101] in their two-year retrospective study did not conduct discounting stating "that costs tended to occur in the first year, making discounting unnecessary….the exact timing of post-operative benefit accrual was unknown" (Derrett et al[101]). Discounting is important in cost-effectiveness analyses as it converts future costs into present values, thereby allowing comparisons between costs and benefits that occur at different times. This is especially important for different interventions where costs usually occur in the current time period, whilst benefits are usually not evident until some point in the future; hence, discounting should have been undertaken by Derrett and colleagues[101] because the study length was greater than one year.

The results and the conclusions offered by each study differed: Derrett et al [101] found that the average cost was higher for ACI compared with mosaicplasty (£10,600 vs. £7,948 in 2003/04 prices).Outcomes in terms of EQ-5D were better for the ACI group compared with mosaicplasty (0.64 vs. 0.47), this difference was not statistically significant. Overall, the incremental cost-effectiveness ratio (ICER) for providing ACI relative to mosaicplasty was £16,349.

Gerlier and colleagues[102] found that the mean costs of ChondroCelect ACI were higher compared with microfracture (€29,808 vs. €9,006 in 2008 prices), but the overall mean QALYs were also higher for the ACI group (21.08 vs. 19.79). The authors found that the probability of ACI being cost-effective was approximately 80% if the payer has a willingness to pay €22,000 per QALY. The cost per QALY gained for ACI over microfracture was €16,229.

Samuelson and colleagues[103] found that the total costs of ACI-C were slightly higher than ACI-P – a difference of $188 ($66,940 vs. $66,752); however, there was some conflicting evidence when they later say that ACI-C was less expensive by $941. The earlier figure we presume relates to the initial cost difference and the latter figure must be after the model was run for 10 years – however, this was not explicitly stated. Also, no further information or breakdown was provided by the authors to show how these costs were obtained or calculated. Individual QALY means were not reported over the 10-year period, except the authors stated that ACI-C was more effective by 0.07 QALYs. The authors calculated a cost per QALY for each of the two different ACI interventions by dividing the cost of the intervention by the QALY to get a cost per QALY; however, this was not an incremental cost. Also, we could not work backwards to find out what these individual costs and QALYs where for each intervention. From the information gleamed from the paper, the incremental cost-effectiveness ratio should have been reported as the cost per QALY gained of ACI-C relative to ACI-P is $13,443 ($941/0.07).

Koerber et al[104] reported mean costs and QALYs for each intervention separately; the costs ranging from €13,445 (microfracture) to €21,204 (MACI) and QALYs ranging from 19.47 (mosaicplasty) to 19.80 (MACI). The cost per QALY gained was worked out for each intervention in relation to microfracture, the authors found that mosaicplasty was dominated by microfracture (microfracture was cheaper and more effective). Whereas the cost per QALY gained ranged from €40,523 for ACI-C to €56,370 for ACI-P both in relation to microfracture.

Sensitivity analyses are important in economic analyses as they deal with uncertainty around key parameters and assumptions made in the model and help confirm the robustness of the results. All four studies conducted some sort of sensitivity analyses ranging from the most simplistic one-way sensitivity analyses (Derrett et al[101]) to the more sophisticated probabilistic analyses (Gerlier et al, .[102]; Koerber et al[104]).

All four peer-reviewed journal articles had some methodological shortcomings. For example, the study by Derrett et al[101] which was a retrospective, cross-sectional study, patients were not randomly assigned to treatment groups and follow-up was for only 2 years. The perspective of the economic analysis was not stated and both costs and benefits were not discounted; only one sensitivity analysis was carried out which looked at the lowering the costs of the ACI (where the ICER decreased slightly), and there were no pre-operative utility scores for both groups (therefore utility values from a waiting list group were used). Gerlier et al[102] felt that there were not enough data on the probability and time to occurrence for specific events such as TKR which meant that a Markov model could not be developed. Another key limitation was the lack of long-term clinical follow-up data which could be used in the model; however, one of the strengths of the study was the use of the data from the RCT

to help populate the model. The limitations in the study by Samuelson et al[103] are most notably the inability to calculate the ICER (cost per QALY gained of ACI-C relative to ACI-P) accurately, short follow-up (10 years), perspective of the economic analysis was not stated, lack of trial data and the model relied heavily on assumptions and data from different studies in the literature, lack of data on the quality of life i.e. the authors assumed utility values after both ACI-C and ACI-P were the same, as where the failure rates. Koerber et al[104] did not explicitly evaluate ACI, but merely used ACI as an example to explain early evaluation and value-based pricing of regenerative medical technologies; although they did provide a supplementary file with some of the model inputs.

The quality of the reporting of the economic analyses by the four articles was assessed using the 27 point CHEERS checklist (Husereau et al[99]). Koerber et al did not identify the study as an economic evaluation in the title nor did it provide a structured abstract (Koerber et al[104]) (see Appendix IX B1). Only two studies reported the viewpoint of the economic analysis (Gerlier et al[102] Koerber et al[104]). Samuelson et al[103] did not describe all the comparators fully. The choice of health outcomes was well reported by all four studies; in terms of analytical methods and study parameters these were best reported by Derrett et al[101] and Gerlier et al[102]. The article by Gerlier and colleagues[102] was the most comprehensively completed in terms of economic analysis using the CHEERS checklist: 18 of the 27 statements (66.7%) were a yes, 4 statements (14.8%) were partially completed, two statements (7.4%) were not completed and three statements (11.1%) did not apply. The least comprehensive article in terms of the economic analysis was the article by Koerber et al[104] in which their study resulted in yes only to 7 of the 27 statements (25.9%), 8 statements were partially completed (29.6%), five statements were not completed (18.5%) and 3 statements did not apply (11.1%).

Using the adapted Phillips et al[100] 32-point checklist to critical appraise the economic models, overall the four articles adequately reported: the objective of the model evaluation, the structure of the model, the type of model for the decision problem, the methods and assumptions to extrapolate short-term results into final outcomes, and the costs used in the model (see Appendix IX B2). The models did not provide clear justification if any feasible options were excluded, the cycle length was not explicitly stated in any of the studies, the choice of baseline data was not justified, none of the methods used expert opinion and neither did any of the models apply a half-cycle correction and its omission was not justified. Again, the article by Gerlier and colleagues[102] was the most comprehensive analysis when using Philips et al[100] checklist to critique the article: 21 of the 32 statements (65.7%) were a yes, 5 statements (15.6%) were partially completed, and six statements (18.8%) were not completed. The article by Samuelson et al[103] was not as comprehensively completed in terms of the economic model: only 8 of the 32 statements were a yes (25.0%), 10 statements (31.3%) were only partially completed and 9 statements were not completed (28.1%).

We also note an Austrian HTA report by Kunzl and colleagues from the Ludwig Boltzmann Gesellschaft HTA unit which commented that Austria was one of the few countries that funded ACI.[105] However the LBG HTA report concluded that in 2009 there was a lack of evidence that ACI was more clinically effective than the other options. No cost-effectiveness analysis was performed.

3.4 Discussion

The cost-effectiveness search highlighted six studies which had been published since 2004; these studies were classed as full economic evaluations on the use of ACI, microfracture and mosaicplasty for repairing symptomatic articular cartilage defects of the knee. These studies included two technology assessment reports – one from the UK (Clar and colleagues[3]) and one from Australia (MSAC[30]). In addition, there was one cross-sectional study from the UK and three economic modelling studies (one each from Belgium, Germany and the USA).

All the articles had shortcomings. The main limitations are summarised below:

- All models (including the Clar et al [3] study) were decision models and no models were Markov-type models. A Markov model is more appropriate than a decision model due to the nature and progression of the disease and because articular cartilage defects can evolve over time.
- There was a lack of long-term clinical follow-up data and any studies with trial data were only for short periods (i.e. 2 years). The model would ideally need two time horizons: a short-term model (i.e. 3 years) to look at the short-term benefits of ACI and its comparators and a long-term model (i.e. 40 years) to look at the longer-term benefits of ACI and its comparators and the need for total knee replacement.
- The models didn't take into account all the various health states that a patient with symptomatic articular cartilage defects of the knee can progress through over time.
- As all the economic models were decision models, transition probabilities were not reported. These probabilities are important for Markov models as it shows the direction and speed of transitions between the different health states.
- There was also a lack of good quality of life data in each of the studies and different instruments and methods which were used in estimating utilities/QALYs were not always reported. Good quality of life data is important to show the benefits which evolve over time from ACI and its comparators.
- Finally, not all resource use, costs and price years were reported. Good resource use and cost data are important as technologies are always evolving and accurate costings are needed to make comparisons with other treatments/interventions.

Table 4. Study characteristics

Author **Publication year** **Country**	**Aims, study design and patient group**	**Economic evaluation type, model, perspective & currency and price year**	**Costs and outcomes**	**Results**
Derrett et al 2005[101] Country: UK	Aim: To assess costs and health status outcomes after ACI and mosaicplasty Study design: Cross-sectional retrospective study Patient group and numbers: - 53 ACI recipients - 20 mosaicplasty recipients - 22 ACI waiting list (ACI WL) recipients Mean age (% male): - ACI: 31.9 (53%) - Mosaicplasty: 34.9 (45%) - ACI WL: n/a (59%)	Type: Cost-utility analysis Model: None Perspective: Not stated Currency and price year: UK £ - 2003-2004 prices Time horizon: 2 years Discounting: None	Resource use and costs: Operations/treatments, arthroscopies, inpatient stay, day case and outpatient visits, MRI scans, histology and x-rays Outcomes: - Modified Cincinnati Knee Rating System - Pain Disability Index - EQ-5D-3L used to calculate QALYs Sensitivity analyses: One-way	Outcomes - EQ-5D means: - ACI = 0.64 - Mosaicplasty = 0.47 Costs: - ACI = £10,600 - Mosaicplasty = £7,948 ICER: - £16,349 cost per QALY
Gerlier et al 2010[102] Country: Belgium	Aim: To assess the cost-effectiveness of ACI with ChondroCelect (CC) compared with microfracture.	Type: Cost-utility analysis Model: Decision tree	Resource use and costs: Reimbursed drugs, medical procedures including ACI with CC and microfracture,	Outcomes - QALY means: - CC = 21.08 - Microfracture = 19.79 Costs:

	Study design: Decision tree model Patient group: Adult patients < 50 years of age with symptomatic cartilage lesions of the femoral condyles who had not developed osteoarthritis	Perspective: Global healthcare payer (public payer reimbursement plus possible patient co-payment) Currency and price year: Euro's € - 2008 prices Time horizon: 5 and 40 years Discounting: Costs - 3%; Effects - 1.5%	consultations, hospitalisations and follow-up Outcomes: - Knee injury and Osteoarthritis Outcome Score (KOOS) - SF-36 collected from an RCT used to calculate QALYs Sensitivity analyses: One-way, two-way and probabilistic	- CC = €29,808 - Microfracture = €9,006 ICER: - €16,229 cost per QALY
Samuelson et al 2012[103] Country: USA	Aim: To assess the cost-effectiveness of ACI-C vs. ACI-P Study design: Decision tree model Patient group: Adult patients (30 years of age) with a focal chondral injury which satisfies the	Type: Cost-utility analysis Model: Decision tree Perspective: Not stated Currency and price year: US$ - price year not stated Time horizon: 10 years	Resource use and costs: Initial consultation, follow-up visits, surgical costs, ACI, physical therapy, medical equipment Outcomes: - Lysholm knee score - Utility values from literature used to calculate QALYs Sensitivity analyses:	Outcomes: - ACI-C = not stated - ACI-P = not stated Costs (total): - ACI-C = $66,940 - ACI-P = $66,752 ICER: - Not calculated

	conditions for ACI repair	Discounting: Costs – 3%; Effects – 3%	Threshold	
Koerber et al 2013[104] Country: Germany	Aim: To assess cost-effectiveness of mosaicplasty, ACI-P, ACI-C, MACI compared with microfracture Study design: Decision tree model Patient group: Patients aged 32 years with symptomatic, isolated cartilage defects and no contra indication.	Type: Cost-utility analysis Model: Decision tree Perspective: German statutory health insurance Currency and price year: Euros € - price year not stated Time horizon: 47 years Discounting: Costs – 3%; Effects – 3%	Resource use and costs: Surgical treatments, inpatient stays, outpatient visits, arthroscopy, revisions, GP visits, imaging, physiotherapy and medications Outcomes: - Utility values from literature used to calculate QALYs Sensitivity analyses: Probabilistic	Outcomes - QALY means: - Microfracture = 19.66 - Mosaicplasty = 19.47 - ACI-P = 19.76 - ACI-C = 19.79 - MACI = 19.80 Costs: - Microfracture = €13,445 - Mosaicplasty = €17,774 - ACI-P = €19,082 - ACI-C = €18,713 - MACI = €21,204 ICER: Cost per QALY gained in relation to Microfracture - Mosaicplasty is dominated by microfracture - ACI-P = €56,370 per QALY gained - ACI-C = €40,523 per QALY gained - MACI = €55,421 per QALY gained

4 Chapter 4. Commentary on submissions by manufacturers and by the Oswestry group including data from the ACTIVE trial

4.1 ChondroCelect

The submission on ChondroCelect was prepared by Swedish Orphan Biovitrum AB on behalf of Tigenix. ChondroCelect was developed by TiGenix, a cell therapy development company based in Belgium. (www.tigenix.com). It was approved by EMA in 2009, and the commercial launch in Europe was in 2010. The first country to approve reimbursement was Belgium in 2011, followed by The Netherlands in 2012. ChondroCelect was licensed to be marketed in Europe by Swedish Orphan Biovitrum (Stockholm) in 2014.

The submission starts with a concise and accurate account of cartilage structure and defects, and treatment options. It then goes on to present evidence of clinical effectiveness from four sources;

- The randomised controlled trial TIG/ACT/01/2000. (TIG is short for Tigenix)
- A "compassionate use" case series.
- A "non-interventional" study – a registry based cohort from routine care in Belgium and the Netherlands where ACI is funded, with 153 patients reaching 6 months or more of follow-up.
- The Belgian reimbursement scheme.

The submission notes the evolution of ACI over time. The TIG/ACT trial used the Brittberg technique using a periosteal flap (ACI-P). The compassionate case series used the same technique but with a collagen membrane (ACI-C). The manufacturer notes that current ACI mostly uses a cell-loading technique. The cells are loaded into the membrane by the surgeon.

As explained earlier, we regard ACI-P as obsolete because it requires more theatre time and has more subsequent costs (shaving of hypertrophy) but no clinical advantage.[54] However we give details of the TIG/ACT trial below. It was a good quality trial but results may now be better, with ACI-C. We also give an account of the compassionate use case series and the other sources.

The product used in both trial and case series had "characterised" chondrocytes.

4.1.1 Trial data: ACI-P versus MF – TIG/ACT/01/2000

This trial compared ACI-P with characterized chondrocyte implantation (CCI) against MF in patients with symptomatic cartilage defects of the femoral condyles. The 5-year results are reported by Vanlauwe et al 2011.[40] Other papers from this study include Saris 2008[66] and Saris 2009.[67] The former provides 12 and 18 month follow-up results and the latter has 36 month follow-up results.

Patient characteristics

Patients were aged between 18 and 50 years with a single symptomatic cartilage lesion (ICRS grade III or IV) of size between 1 and 5 cm^2 in the femoral condyles of the knee and gave consent to follow a strict rehabilitation protocol.

118 patients were randomised, 57 to the ACI-P CCI group and 61 to the MF group. Six of the ACI patients were withdrawn because of failed chondrocyte expansion (n=1) or negative ChondroCelect (CC) score (n=5), (CC score helps predict whether the cells can grow into stable hyaline cartilage in vivo) so only 51 patients were included in the analysis. Details of baseline characteristics of these patients are from previous studies – Saris et al 2008/2009.[66, 67] The mean ages of patients were similar in both groups (33.9 years). Most patients were male (61% in ACI and 67% in MF). Mean weights were similar (78.3 kg in ACI, 80.6kg in MF, BMI not reported). Median durations of symptoms were similar (1.97 years in ACI, 1.57 in MF). 37% in ACI and 21% in MF had had more than two previous knee procedures. In the ACI group, five had had previous microfracture, three had had subchondral drilling, and one had had abrasion arthroplasty. Only 12% of patients in ACI and 23% in MF groups had no history of previous knee surgery, including arthroscopy. At baseline arthroscopy, 98% of patients in ACI and 97% in MF had a single cartilage lesion, mostly grade IV lesions. Mean sizes of defects after debridement were 2.6 cm^2 in ACI and 2.4 cm^2 in MF.

More information is available in the paper by Vanlauwe and colleagues [40]. Patients in each group were categorised into re-intervention (RIG) or no re-intervention groups (NRIG) based on whether they underwent re-intervention on the index lesion during the study period. Seven patients in the ACI group and 10 patients in the MF group underwent re-intervention on their index lesion mainly because of recurring pain. In the ACI group, 5% patients in the NRIG group and none in the RIG group had BMI of >30 kg/m^2.

Details of intervention and comparators

Details of intervention and comparators were given in Saris et al 2008/2009. All patients underwent baseline arthroscopy to assess eligibility to participate in the study. Patients in the MF group were treated following a technique recommended by Steadman and colleagues[98] and those allocated to the

ACI group were treated following the method recommended by Brittberg and colleagues.[19] Patients allocated to ACI group had cells implanted about 27 days after initial arthroscopy, secured beneath a periosteal flap.

Patients from both groups underwent an identical rehabilitation programme. In the first two weeks after surgery, patients were not allowed to bear any weight on their operated knee. After this, they were allowed to bear weight of up to 10-15 kg in the third week and in the fourth to sixth weeks the weight was increased up to 15-30 kg. Then, the weight was increased progressively as long as patients could tolerate it. For the first eight weeks, all patients wore an unloader brace.

Duration of follow-up

Patients were followed up for 60 months

Outcomes

At 12 months, cartilage biopsies were collected via arthroscopy from the middle of the repaired tissue for histopathological analysis. The primary outcome measure was change in overall KOOS score from baseline at 36 months and 60 months. Other outcomes included adverse events, changes from baseline in different KOOS domains, and analysis of overall KOOS after adjusting for the baseline covariates overall KOOS, age, associated lesions and lesion location. Exploratory analysis was undertaken according to the time since onset of symptoms (<3 years or ≥3 years) and age (<35 years vs. ≥35 years).

Treatment failure was defined as '*a reintervention affecting more than 20% of the index lesion'*. Time to treatment failure was defined as '*the time between the end of the surgical procedure and the date of failure or reintervention'*. All treated patients were included in the efficacy and safety population.

Results

KOOS results were available from 43 patients in the ACI group and 45 patients in the MF group at both 36 and 60 months. (To recap, an increase in KOOS score indicates improvement. A score of 100 indicates no symptoms, a score of 0 is worst possible.)

Table 5. Mean change in overall KOOS score and subscales* from baseline at 60 months

	60 months (total group)		
	ACI (SE)	**MF (SE)**	**Difference (95% CI, p value)**
Overall KOOS	21.17 (2.88)	14.07 (2.54)	7.10 (-0.52 to 14.73; p=0.068)
Activities of daily living	16.42 (2.97)	11.35 (2.62)	5.07 (-2.79 to 12.94; p=0.203)
Pain	19.04 (3.17)	13.27 (2.74)	5.77 (-2.55 to 14.09; p=0.172)
Symptoms/stiffness	17.70 (2.82)	10.90 (2.52)	6.81 (-0.70 to 14.32; p=0.075)
Quality of life	32.12 (4.30)	21.23 (3.87)	10.89 (-0.59 to 22.38; p=0.062)
Function, sports and recreational activities	32.50 (5.88)	22.98 (5.69)	9.52 (-6.87 to 25.90; p=0.250)

*All sub-scales range from 0 to 100

At 60 months follow-up, the overall KOOS score and its subdomains improved in both treatment groups (Table 6). The difference between the two groups was not statistically significant (7.10 95% CI -0.52 to 14.73; p=0.068). In both treatment groups, the improvement in mean KOOS score started as early as six months and was maintained up to 60 months follow-up (Table 6).

Table 6. Mean change in overall KOOS score from baseline

Time-point	**ACI**	**MF**
Baseline	56.30	59.53
	Change from baseline	**Change from baseline**
6 months	14.27	13.18
12 months	16.96	13.54
18 months	18.45	15.5
24 months	19.38	13.09
30 months	20.71	15.16
36 months	21.35	14.72
60 months	21.17	14.07

In the subgroup analysis according to the duration of onset of symptoms, the mean improvement in KOOS score was greater in the ACI group than MF in patients with onset of symptoms <3 years duration (25.96 (SE 3.45) vs. 15.28 (SE 3.17); difference: 10.69 (95% CI 1.30 to 20.07, p=0.026)). There was no significant different in the mean KOOS score between the groups in patients with onset of symptoms >3 years duration (ACI: 13.09 (SE 4.78) vs. MF: 17.02 (SE 4.50); p=0.554).

Subgroup analysis by age found no statistical difference between the treatment groups (younger age patients <35 years: ACI 22.4 (SE 3.70) vs. MF 16.59 (SE 3.55); p=0.262; patient aged 35 years and more: ACI 19.61 (SE 4.51) vs. MF 15.16 (SE 4.01); p=0.465).

Seven patients (13.7%) in the CCI group and ten patients (16.4%) in the MF failed the treatment and had to undergo revision surgery on the index lesion. Most of the failures in the MF group occurred in the first three years while those in the ACI group occurred in the fourth year or later. The Kaplan Meier (KM) figure (Figure 3 in the published paper) depicting time to failure has been reproduced below (Figure 2).

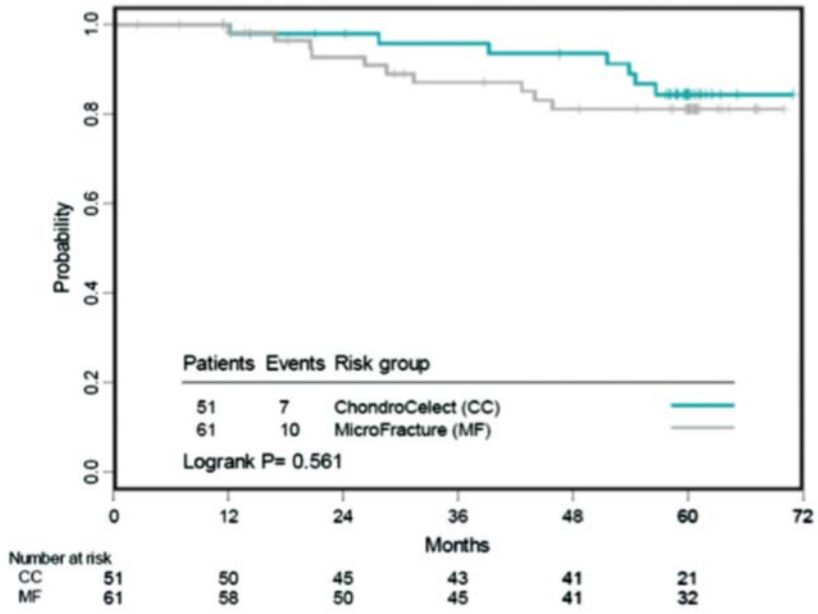


Figure 2. Time to failure (reproduced from the published study)

The number of failures was lower in male patients than in female patients (ACI: 6/19 females vs. 1/32 males; RR 4.21 95% CI 1.03 to 17.57; MF: 7/20 females vs. 3/41 males; RR 4.78 95% CI 1.49 to 15.62).

Radiographic results of 49 patients taken at baseline and at 60 months were available. The Kellgren-Lawrence score, which is a method of grading severity of knee osteoarthritis, showed no difference between the two treatment groups at 60 months.

More patients in the ACI group experienced at least one related AE than those in the MF group (82% vs. 62%) during the five years. The AEs were mild to moderate in intensity. The most common AE reported was arthralgia (75% ACI vs. 62% MF in first 3 years; 36-60 months – ACI 14% vs. 4% MF). Other AEs included joint swelling (22% in ACI and 7% in the MF group in first three years; from 36-60 months 0% in CCI and 2% in MF group), joint effusion (12% in ACI vs. 2% in MF between 36 and 60 months). None of the effusions were categorised as severe.

There were three AEs classed as serious in the ACI group considered related to treatment; one deep vein thrombosis, one arthralgia and one tendinitis.

At the end of the follow-up, most of the AEs had disappeared but there were 3/37 cases and 1/40 cases of effusion in ACI group and MF respectively.

Commentary
Better results were seen with ACI in patients with shorter duration (< 3 years) of chondral defects.

4.1.2 Case series.

The baseline characteristics of patients in the case series were more varied in some ways than in the RCT, as shown in Table 7.

Table 7. Comparison of baseline characteristics trial and case series patients

	RCT	**Case series**
Age mean (range)	34 (18-50)	34 (range not given)
Male %	64%	57%
Duration of injury	Median 1.57 yrs, range 0-18	
Site	Femoral condyles	Medial condyle 43%, patella 19%, lateral condyle 15%, trochlea 9%, condyle unspecified 7%
Previous procedures	88% in ACI group, with 37% having had 2 or more, “in particular marrow stimulation”	Not reported
BMI > 30	10%	.
Mean BMI		25
Mean weight	81kg	

Inclusions	Symptomatic single lesion of femoral condyles. Between 1 and 5 cm^2 in size.	No predefined entry criteria.
Exclusions	Significant knee abnormalities, patellar lesions, OA, previous mosaicplasty, MFX in previous year	Active infection at biopsy site, significant OA, drug allergies
Size of lesion	1-5 cm^2	3.5 cm^2 (0.2 – 20)

The outcomes in the compassionate use case series were the Clinical Global Impression measures of improvement (CGI-I) and efficacy (CGI-E). CGI-I measures change from baseline (no change, improvement, worsening). CGI-E has 4 points: very good, moderate, slight, no change or worse. Results were divided into short-term follow-up (under 18 months, mean 9 months, which is too short for best outcome) and longer term (> 18 months, mean 27 months) but figures in each group are not given.

Note that these scales are reported by the surgeon not the patient. The CGI-I results were reported as showing good outcomes (much improved or very much improved) in 68%, with serious worsening in only 2%. The CGI-E results showed 38% with very good results, 36% with moderate improvement, 12% with slight improvement, and 11% unchanged or worse. (From table 10, page 30 – results total 97 not 100%)

The submission reports that no differences were seen by duration of follow-up (< 18 months vs >18 months), site of lesion (patella versus condyles) or size of lesion (small vs large, not defined). Patients with single lesions did better than those with multiple ones, but only significantly so in CGI-I results (improved 86% vs. 77%). Results in multiple lesions were good.

The commonest adverse event was knee pain (24%) and 54% had no AEs. As expected with the ACI-C method, few patients (2%) developed cartilage hypertrophy.

4.1.3 Registry cohort.

Details from this cohort are sparse (pages 32 – 34) and only about half the cohort (153 of 308) have 6 months or more of follow-up. The mean age of 32 (range 15- 50) is similar to RCT and compassionate use case series. The only benefit reported is an increase in KOOS, at up to 36 months, but numbers at each follow-up period are not given. Adverse event data comprise 5 (table 12) or 6 (text below, page 33) treatment failures, and two DVTs amongst a total of 17 serious AEs (but no denominator given).

Treatment failure was defined as the need for a re-intervention for more than 20% of the treated area, associated with symptoms. The summary states that no new AEs were reported in the registry cohort.

4.1.4 Belgian reimbursement scheme

Little information is reported from this source. Two procedures failed within 12 months and another 2 failed between 12 and 24 months, in 254 patients. Only 51 patients had reached 3 years of follow-up. The data show an increase in numbers treated, from 51 in the first year (May 2011 – April 2012), 93 in the second and 110 in the third, possibly suggesting levelling off in numbers. The population of Belgium is 11.2 million, so the 3rd year rate is about 10 per million per year. The equivalent numbers per year in England would be 540, and in Wales 30.

The ChondroCelect submission(page 34) argues, with some justification (see chapter 2 of this report), that ACI is more successful as primary procedure than in patients who have had previous MF. The Minas study[72] is cited in support of the assertion.

4.1.5 Cost-effectiveness.

HRQoL was measured using the SF-36 questionnaire which was administered at the following time points: 18, 24, 30, 36, 48 and 60 months post procedure. At 36 months SF-36 scores were slightly better for ACI. However, the submission did not provide a total score for the SF-36 scores.

Introduction and model structure

The economic analysis by the manufacturers used a *de novo* Markov model to assess the cost-effectiveness of ACI in relation to MF from an NHS and Personal Social Services (PSS) perspective. Both costs and outcomes were discounted at a rate of 3.5% per annum in line with NICE guidelines. Only the written assessment was provided to ERG. The model used is simpler than the Warwick one but is regarded as fit for purpose.

Microfracture was considered to be the only relevant comparator for ACI and other comparators such as mosaicplasty were not considered for this analysis – this is a reasonable assumption. The submission states that mosaicplasty is little used and "not recommended by NICE". The last assertion is not quite correct. The NICE Interventional Procedures Guidance (2006)[32], which is concerned only with safety and efficacy (not cost-effectiveness), states that there were no major safety concerns, and mentions; "some evidence of short-term efficacy but data on long-term efficacy inadequate." Evidence of benefit came from an RCT with only one year of follow-up, in which ACI was better, and from case series with 2 or 3 years follow-up. NICE recommended that mosaicplasty should be used

only with “special arrangements for consent and audit or research”. So it is correct to say that NICE has not recommended mosaicplasty in routine care.

The model is similar to the Warwick assessment group model where patients enter the model at the time they receive the procedure (ACI or MF). However, there are differences between the Warwick model and this submission: the cycle length used in the submission model is 1 month, whereas the Warwick model used a cycle length of one year. The average age of patients receiving a procedure in the submission model is 33 years and the model has time horizon of 75 years – on this basis the model assumes that patients can live up to an average age of 108 years (however, they did state by this point >99.9% of patients will have died). The model is separated by gender, but we know that there is no difference is the success or failure of the two different procedures if lesions are comparable.[106]

The model structure is logical and similar to the Warwick model as it allows both temporary and permanent successes. If either MF or ACI fail, the patient has debridement to remove the damaged tissue and can go on to receive another repair, but this second repair is MF only. Otherwise the patient may choose not to have a repair and are offered conservative pain relief treatment only. If this second repair (MF) fails, the patient will receive debridement and pain relief only.

Patients who receive best supportive care, may deteriorate and are assessed for a TKR. The submission model assumes that a patient can only receive up to a maximum of three TKRs. The modelling uses time to treatment failure as the outcome that drives the ICERs, using 5-year data from the TGC/ACI RCT and the compassionate use case series. Delaying treatment failure leads to postponement of TKR costs. If the second TKR fails then the patient receives just analgesics. The following is unclear from the submission model:

- The average age that a patient will require a TKR
- As evidence has shown, some patients may receive more than two TKRs.
- Also, the first knee replacement can either be partial or a total KR. As described later, this affects the costs of the second replacement.

Finally, the model assumes that patients can die at any stage from all-cause mortality, and there is a low risk of mortality from undergoing a TKR or a TKR revision.

Model inputs

1. Efficacy of first treatment

The model uses time to treatment failure (TTF) as a proxy measure of treatment efficacy (i.e. when a new procedure for the same defect was required). This information on time to treatment failure (i.e. transition probability for moving from primary treatment success to treatment failure) was obtained

from Kaplan-Meier plots as reported in the Vanlauwe et al article.[40] This article reported that ACI was better than MF and that patients in the ACI group waited longer before needing a further procedure due to the longer benefits. This is a reasonable assumption for the model.

Four different scenarios were used for the TTF after the observed data: Scenarios 1 to 3 assumed no ACI benefit after the observed data, or after 10 or 20 years, at which point then the benefit of MF is applied to the patient cohort. Scenario 4 used the line of best fit for the entire model duration. For all scenarios (as shown in the figures 16 to 19), ACI was better than MF; again these scenarios seem plausible.

Another four different scenarios were also used for treatment failure using observational ACI data (to take into account a normal clinical setting rather than a trial setting). The observed failure rates for ACI were 0.79%, 1.39% and 0.00% in years 1, 2 and 3 respectively. A weighted average failure was calculated as 0.89% and this was applied. Scenarios 1 to 3 assumed no ACI benefit after the observed data, or after 10 or 20 years, and in scenario 4 it was assumed that the average ACI benefit was maintained.

2. Subsequent treatment

The submission model in the base-case analysis assumed, based on clinical advice, that when ACI fails that 90% of the patients will receive MF and when MF fails that only 5% of patients receive another MF. As the manufacturers said this latter value is too low (these values are set to 50% in the sensitivity analysis). The submission did not explicitly state the reasons why patients who receive a first MF are less likely to receive second MF compared to patients who receive a ACI first.

Two papers from the TIG/ACT/01/2000 trial reported failure rates for subsequent MF: Vanlauwe et al [40] reported MF failure rate of 16.4% at 5 years (converted monthly rate 0.30%) and Saris et al[67] reported MF failure rate as 11.5% at 3 years (converted monthly rate 0.34%). The latter value was used in the sensitivity analysis. The submission assumed based on clinical advice that a second MF following a first MF would be half as effective i.e. twice the failure rate.

Two studies which reported failure rates for debridement were used for best supportive care (BSC) following initial and subsequent treatment failure in the analysis: Forster et al[107] reported a failure rate of 20.0% at 1 year (converted monthly rate was 1.84%) and Bernard et al[108] reported a failure rate of 18.0% at 5 years (converted monthly rate was 0.33%). The latter value was used in the sensitivity analysis. There is a typo on page 44 and should read – "… applying the lower failure rate (0.33% per month)…" instead of (1.84% per month). Failure of BSC leads to knee replacement.

For TKR, based on expert clinical advice the submission model assumed that 95% of the cohort would be suitable for a TKR and that a TKR is expected to last for 10 to 20 years (a midpoint of 15 years was used in the base-case submission model and was converted into a monthly transition probability). For those patients that need a TKR revision, the model assumed that there was a slightly higher failure rate than the first TKR and the first TKR will only last for 10 years - these are plausible assumptions for this patient group.

3. Mortality

The manufacturers used Office of National Statistics data for all-cause mortality (split by age and gender) and for the base-case TKR mortality data was based on a figure reported on the NHS Choices website [109] (1.6%). A paper by Mahomed et al[110] was used for TKR mortality (0.7% for initial TKR and 1.1% for a revision TKR) in a sensitivity analysis. As the NHS Choices website did not report a mortality rate for TKR revision the submission model assumed that this value would be 2.5% (i.e. based on Mahomed et al[110] a 57.1% increased risk). This is a reasonable assumption, as this is a longer operation, patients are older and rehabilitation might be slower.

4. Costs

The costs for the different procedures, rehabilitation, TKR, TKR revisions and pain relief were obtained from UK sources, literature and the HTA report by Clar et al[3]. The cost of procedures included the costs of surgery, inpatient stays and physiotherapy follow-up. The submission stated that cost of TKR could not be identified from the NHS reference costs so they used information from the previous HTA report[3] (whereas the Warwick model uses an NHS reference cost for TKR). The costs which have been inflated from the previous HTA report by Clar et al[3] are underestimated as the wrong base-case year was used: the submission model should have used the year 2003/04 prices instead of 2005/06 prices. The inflation multiplier will have been 1.286 instead of 1.200. For example, the cost for MF as an inpatient procedure should be £3,020 instead of £2,818. The submission reports that "All costs are updated to 2014 using the latest Hospital & Community Health Services (HCHS) index" – when in fact the prices are uplifted to year 2012/2013. We have not amended any of the costs below, as this would mean the total costs and ICER value would be different. However, we believe that the magnitude and direction of the costs differences will not change substantially.

The cost of ACI included the cost of the product including two-way courier and development of cell culture (£16,000) plus the cost of arthroscopy and cell harvest (procedure 1 - £722.45) and arthrotomy conducted in an outpatient setting (procedure 2 - £109.65). However, the cost for implantation of the cells is an under-estimate since the procedure would be done as a day-case not an outpatient visit. The total cost of ACI was £16832.10. Adjustment of the cost of the second procedure gives a total cost of ACI of £16832 + £722 = £17554. The submission model also included the cost of a TKR

assessment which included a GP assessment and cost of an outpatient appointment (£146.65) whether the patient went onto to receive a TKR or not. The cost for TKR and TKR revision (£6,500.85 and £12,093.24, respectively) – look plausible.

The submission model also included the cost of rehabilitation after ACI, MF and TKR in line with the Warwick model. However, the cost used by the manufacturers is lower than the cost used in the Warwick model (£42.47 vs. £256.00). In addition, the submission model also included the cost of pain relief medication – which consisted of paracetamol (this cost was not included as the patients would have purchased this over the counter) and non-steroidal anti-inflammatory drugs (NSAIDs). The manufacturers estimated a weighted average cost for NSAID per month as £9.79. This cost is negligible and has not been included as a cost in the Warwick model.

The model also included a cost for patients who were classed as "unresolved patients". This cost was estimated at £384.43 per year which included the cost of GP visits, treatment visits, medications, outpatient visits, physiotherapist, prescribed aids (not specified but presumably walking aids), complementary (not specified) and other therapies. This total cost was based on patients with lower limb osteoarthritis – however, for some patients this cost may be an over-estimate as some of these patients may just have pain relief medication and choose to put up with the pain.

The different cost values were varied in the sensitivity analysis.

5. Health-related quality of life

The submission states that there is lack of utility data in patients with a knee cartilage defect. Utility scores were based upon on analysis of the SF-36 questionnaires which were collected up to 60 months post-surgery as reported in Gerlier et al[102] in Table II. These are plausible utility values. The submission model also accounted for the decreasing utility over time by using age-related UK population EQ-5D weights as reported by Kind et al.[111] The model assumed that after successful ACI and MF, patients would have the same benefits, and the utility value used after surgery was 0.8170. The model does not specifically state how long this benefit lasts, we can only assume it is five years in line with the Gerlier et al[102] paper. This does not take into account that after MF the utility value will stay at this value for a few years but is likely to decline later, eventually to the pre-surgery value as these patients are most likely to require another repair. Values were varied in the sensitivity analysis.

6. Adverse events

Adverse events were not included as the manufacturers stated that there were no key differences between the two treatment arms.

Model results

The total cost of ACI was £22,586. The total cost of MF was £13,547. This means that the incremental costs are £8,890 and £9,129 respectively and not £8,801 and £8,801 as noted in the submission report. Total QALYs gained for ACI compared with MF were 1.29. The corresponding ICER for ACI compared with MF was £7,077 per QALY (and not £6,997). The main cost drivers were the cost of the cells and the fact that fewer people needed further repair or TKR with ACI compared with microfracture. The model also highlighted that further QALYs are gained by ACI patients when they received a subsequent MF (4.15 more QALYs when looking at QALY results disaggregated by health state), compared to MF patients when they received a subsequent MF (as these patients will fail more quickly).

The sensitivity analyses found that the ICERs for the different efficacy scenarios and the subsequent treatment efficacy scenarios as listed earlier were consistent with the base-case analysis; that is, although ACI was more expensive it was also more effective. For the subsequent treatment scenario in the base-case analysis, the use of subsequent MF after ACI was 90%, but only 5% had a second MF after the first MF (i.e. only a small proportion of patients would receive a second MF). In the sensitivity analysis this value was changed so that 50% would have a second MF after both ACI and MF. The resulting ICER was nearly £25,000. This is due to more people having a MF and the QALY gain being lower (0.46 vs. 1.29).

The ICER was also sensitive to the model time horizon. For example, if a 5-year time horizon was used i.e. 5 years the resulting ICER was approximately £290,000. This was due to the majority of costs of ACI being incurred upfront i.e. in the first few years and the benefits from ACI not being seen till later i.e. fewer people moving to an unresolved state and fewer people in need of a TKR. The model only became cost-effective when the model was run for 20 years (ICER approx. £22,000). The ICER was robust to other scenarios which were tested such as different utility values, TKR mortality and discounting. The probabilistic sensitivity analysis results were similar to the deterministic with ACI probably the most cost-effective around the £6k to £7k range (i.e. a 98.8% chance of being cost-effective).

Overall the model assumptions and results look plausible.

4.2 Aastrom Biosciences submission

Aastrom have now changed their name to Vericel Corporation.
The submission from Aastrom was based mainly on the SUMMIT trial including the extension study up to 3 years (it will in time produce 5-year data). The SUMMIT trial was described in detail in chapter 2.

Data from the Basad study were also presented.
The submission states that an indirect comparison of MACI® and ACI was performed, using microfracture as the common comparator, but this is illustrated by two separate forest plots, one showing the SUMMIT results for MACI® versus MF and the other showing the Saris results for ACI versus MF. Some relative risks for SUMMIT versus Saris are then presented but the underlying methods and calculations are not provided. However results were similar and confidence intervals overlapped with 1. So no claim for clinical effectiveness superiority of MACI® over ACI is made. Data on ACI versus mosaicplasty are presented, and used to argue, reasonably, that MACI is superior to mosaicplasty. (page 92)

Aastrom argue that the main comparator is microfracture, particularly as the lesion sizes considered in the submission (3 to 20 cm^2) are too large for mosaicplasty.

4.2.1 Cost-effectiveness

The submission by Aastrom Biosciences did not provide any cost-effectiveness analyses due to the recent purchase of the MACI® product by Vericel from Sanofi. Cost-effectiveness evidence was presented in the MSAC submission[30] and the manufacturers aimed to adapt this. However, this was not possible due to time constraints, so only a budget impact/costing forecast model was provided.

The budget impact model estimated by Aastrom indicated that 9,549 patients in England and Wales were eligible for cartilage repair in 2013. Of these 9,549 patients as indicated by the NICE scope, 500 of them will be eligible for MACI or an ACI in year 5. The manufacturers assumed that there would be an equal split of the use of MACI and ACI. The rest of the eligible patients would receive microfracture, though the reasons for not offering ACI are not explained. Based on data from 3 studies [Minas 2009[72]; Nawaz 2014[77]; Vijayan 2014[112]] the manufacturers reasonably assumed that re-operations after microfracture do not have the same success rate as primary MACIs or ACIs.

List prices were used for the costs for ACI (£18,300) and MACI® (£16,226 excluding VAT). The cost of microfracture was £2,464 which was obtained from the NHS reference costs.[113] Cost of theatre, surgery for implantation of MACI/ACI was assumed to be the same as the cost of microfracture though our clinical opinion is that MF usually requires an inpatient stay (because of pain) whereas ACI is usually a day case procedure. The Aastrom assumption may therefore slightly disadvantage MACI®. The submission states that (page 157) that patients have one procedure. It is not clear whether this means that they would only have one MACI, or whether it is an error by not accounting for both arthroscopy and harvesting, and later implantation. The manufacturers assumed

that the cost of MACI/ACI reoperation would be £16,226. The cost of initial MF with MACI/ACI as second repair at an average cost of £17,623 also seems appropriate. This extra differential cost approximates to 3.5 extra rehabilitation visits. The cost of rehabilitation was £376, which was obtained from the Unit Costs of Health and Social Care [Curtis, 2013[114]]. This cost was based on a community based physiotherapist where rehabilitation was 6 to 8 sessions, each session lasting 30 minutes. Alternative rehabilitation costs could have been obtained from the NHS reference costs. The budget impact model did not take into account any outpatient visits and any inpatient stays for MACI/ACI.

Three-year probabilities for MACI reoperation and MF reoperation were obtained from the SUMMIT trial data[97] and these were converted to annual probabilities: 0.005 and 0.014, respectively. The annual probability for MACI was also assumed for the ACI reoperation, which seems a reasonable assumption. The Saris 2009[67] data provided alternative three year probabilities for reoperation – these were converted to annual probabilities: 0.010 for ACI/MACI reoperation and 0.040 for MF reoperation. The manufacturers assumed that if MACI/ACI failed then a reoperation would be either MACI/ACI; however, if MF failed than a reoperation would be MACI/ACI.

The budget impact model explored two scenarios: one scenario with MACI/ACI as first line treatment and the other scenario without MACI/ACI (with MF only). Using failure rates based on the SUMMIT data[97] there were total cost savings from using MACI/ACI ranging from approx. £5.9 million in year 1 to £8.3 million in year 5 – this was due to the lower reoperation rate and the expectation that 500 procedures (of the approximate 10,000 procedures) were either MACI/ACI. There is a typo on page 157 and this should read "…the impact if MACI/ACI amounts to £5.9m rising to £8.3m in year 5" instead of "…the impact if MACI/ACI amounts to £3.7m rising to £8.3m in year 5". The submission also included a budget impact model using the higher failure rates from Saris (2009).[67] There were further total cost savings although lower than the cost savings when the SUMMIT trial[97] failure rates were used - using MACI/ACI the cost savings ranged from approx. £5.8 million in year 1 to £7.8 million in year 5 – these lower cost savings were due to the need for more reoperations after MF. In conclusion. The cost calculations provided by Aastrom Biosciences seem reasonable and plausible.

4.3 Submission by Oswestry

The Oswestry submission was received by Warwick on 16th September. It includes interim data from the ACTIVE trial, which has about 5 years to run.

4.3.1 The ACTIVE trial

The ACTIVE trial is a MRC-funded multicentre randomized controlled trial of ACI against standard treatment which could include debridement, abrasion, drilling, MF, mosaicplasty or bone graft (according to surgeon's discretion) in 390 patients (195 in each group) with a symptomatic chondral defect(s) on the medial or lateral femoral condyle or trochlea/patella who have failed previous treatment and who were also considered suitable for ACI/MACI.[33]

Patients were recruited from 29 centres. Some centres recruited very few patients. The RJAH Hospital in Oswestry recruited 87 patients (22%). Six centres recruited between 20 and 29 patients, and another six recruited between 10 and 19. The other 16 centres recruited under 10 patients each.

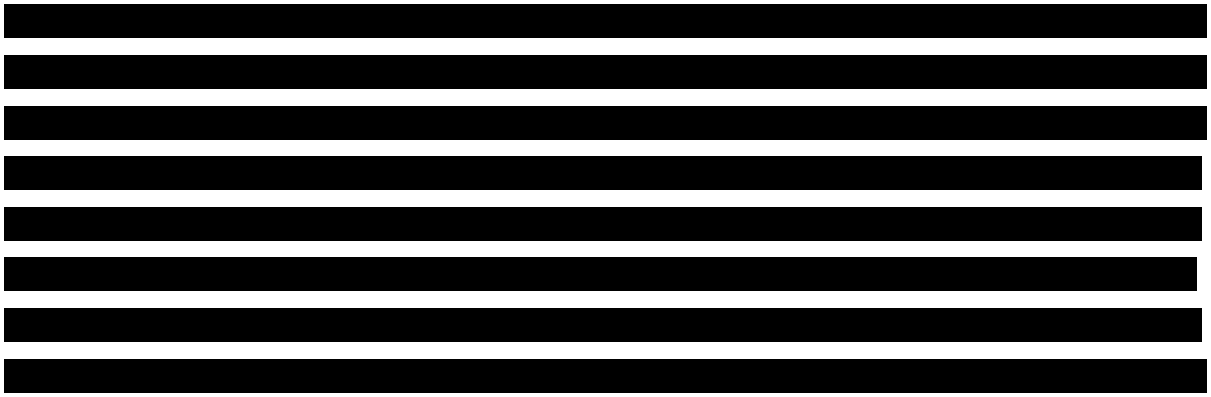
There were two sub-randomisations, the first (n=99) to compare use of periosteum against collagen caps, and the second (n=9) to compare two types of MACI – MACI and Chondron.

Quality assessment

Using the modified Coleman methodology score, the study scored a total of 73 suggesting that the quality is good. Some information was not available in the submission, but was available in the protocol. There was no information on relative risk reduction, absolute risk reduction or number needed to treat.

The cells used came from two sources. In the Oswestry centre, the locally produced cells were used, but in all other centres, commercially produced cells (all from Genzyme?) were used. So ACTIVE is a trial of "traditional ACI" only in the Oswestry centre.

The first primary outcome was to have been time to cessation of benefit, but this proved difficult to measure, and the second primary outcome, Lysholm assessor outcome score, was used. (The submission uses the phrase "independently assessed".) Other outcome measures included patient-assessed Lysholm score, Cincinatti knee score, IKDC score and EQ-5D.



[redacted]

In the clinical effectiveness section, results are given for up to 5 years of follow-up. However later data are used in the cost-effectiveness section. [redacted] Over the five year period, [redacted] with failure defined broadly, including presence of symptoms [redacted].

[redacted]

The Lysholm score assessed by investigators [redacted]

As part of secondary outcomes, patients were also asked to state their rating of operation at all follow-up points with responses ranging from extremely pleased to much worse.

Table 8. Patients responses

Not all of the listed SAEs look serious. The treatment related SAEs were

There was

4.3.2 REACT study

In addition to the ACTIVE trial, the submission provides results from a cohort of [redacted]

The REACT investigators state that MRI is probably the best non-invasive method to correlate clinical outcome with the graft appearance on MRI, but that MRI does not give a good guide to graft histology or predict future events.

The authors state ACI-C with Chondro-Gide is better than ACI-P as the former leads to repair of the defect with better quality tissue. For this, the submission included evidence from a study (McCarthy and Roberts[115]) comparing the two in 88 Oswestry patients – 55 treated with ACI-P and 33 patients with ACI-C. These patients are presumably a subset of the REACT group.

4.3.3 Cost-effectiveness

The cost-effectiveness analysis by Oswestry was based on the ACTIVE trial data, but using cell costs from Oswestry only. The cells used in other ACTIVE sites came mainly from Genzyme. The

submission provided the costs of ACI and the different comparators. The benefits were in terms of quality-adjusted life years (QALYs) which were estimated from the EQ-5D-3L.

The total costs and incremental costs with and without the market forces factor (MFF) provided in the submission have been summarised in Table 1 below (MFF estimates the unavoidable cost differences of providing healthcare). Within Payment by Results (PbR), the MFF directly funds providers for the relative level of unavoidable costs they face. Each NHS Trust receives an individual MFF value used to establish the level of unavoidable costs they face relative to each other. Accounting for unavoidable costs ensures a level basis across the country to provide equal amounts of healthcare per pound. So in terms of PbR income this would equal the activity multiply by its tariff price and this is then multiplied by the MFF value. All costs are in 2014/2015 prices in UK pounds sterling. The second stage for ACI includes the cost of the cells. Production of cells in Oswestry cost £4125 per patient. The submission stated that the incremental cost of ACI over TKR was £3,746 and the incremental cost of ACI over microfracture, osteotomy or mosaicplasty was [redacted]

Table 9. Costs of ACI and its comparators by Oswestry

Procedure	Costs (2014/15 prices)	Costs including MFF	Incremental costs of ACI over the comparator (including MFF)
Intervention - ACI			
• First stage	£2,398	-	-
• Second stage	£6,876	-	-
Total cost of ACI	£9,274	£9,565	-
Comparators			
Total knee replacement	£5,642	£5,819	[redacted]
Microfracture	£2,396	£2,471	£3,746
Osteotomy	£2,396	£2,471	£3,746
Mosaicplasty	£2,396	£2,471	£3,746

For the ACI procedure they stated that costs included operations, hospital stays, the cells and any further implants. However, for the comparators it was not stated what the costs included. The TKR cost is line with NHS reference costs (2012/2013) where the cost is £5,676 [NHS reference costs 2012/2013.[113]] The costs only included the direct costs of the procedures. No information in the submission was provided on any further outpatient or rehabilitation visits. The submission also stated that further data had been collected using patient diaries on patient and societal costs such as any out-of-pocket expenses and time off work, but were not available in time for this submission.

[redacted]

Numbers of patients and EQ-5D at each year are reported in their Table 20, and data for later years are reproduced in our Table 2.

[redacted]Table 10. EQ-5D scores in ACTIVE trial

	[redacted]		[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

The main criticism is that the QALYs were not reported individually for the different control procedures, most likely due to the small numbers. If QALYs were reported separately for the individual control procedures, this would have allowed a rank comparison and any options which are dominated (or extended dominated) to be excluded from the incremental analysis (this information as we found later was presented in Table 22 in the Appendix). Additionally, the Oswestry submission stated on page 21 "….it is recognised that the EQ-5D, which the calculation of the QALY is based on, is a crude assessment tool". No data on any attempt at mapping to generate utilities to enable QALY calculation are provided, for example, from the primary outcome measure - the Lysholm self-assessment scale to the EQ-5D index.

In the base case, both groups were treated as homogenous, but due to differences in the treatments for the control group and cell sources for the ACI group, further analyses tested for heterogeneity in each group. For the control groups (microfracture, microfracture plus collagen membrane and mosaicplasty), the data from the ACTIVE trial suggested little difference in the EQ-5D scores (presented in a graph). The data in the graph showed that mosaicplasty patients had a faster recovery, but due to the small number of patients the conclusion should be treated with caution, and they probably had smaller lesions. For the ACI group, as the cells came from different sources, the submission included a regression analysis to see whether cell origin might affect their benefit. The regression analysis provided a negative value from which the authors concluded that "ACI patients treated outside Oswestry are unlikely to have more benefit from ACI".

The submission lacks clarity in places. Section 7.2 states that the QALYs were derived from the EQ-5D data, but the numbers of patients in Table II (EQ-5D) and Table III (QALYs) are rather different with more in Table II – for example at 2 years, Control group 147 in Table II versus 115 in Table III. It is not clear how the EQ-5D differences are converted into cumulative QALYs.

The absolute values for EQ-5D from the ACTIVE data often show little difference as shown in Table 10 above, but changes from baseline EQ-5D (Table 11) show a more consistent advantage for ACI.

Table 11. Increases in EQ-5D from baseline, derived from OsCell Table 2

	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

4.4 Discussion – clinical effectiveness

The four main trials described in this review all show some superiority of various forms of ACI over microfracture, but in different timescales and to different degrees. The Basad and SUMMIT trials show clear differences in favour of MACI by two years in Lysholm and KOOS scores respectively. SUMMIT found no significant difference in EQ-5D VAS changes – both groups improved by 17 at 2 years. The TIG/ACT trial shows superiority overall by 3 years. The ACTIVE trial (in which ACI was a mixture of ACI-P, ACI-C and MACI) showed no benefit in most outcome measures at 5 years, but some separation in EQ-5D after that. With the exception of EQ-5D, results are only available to five years in an interim analysis provided for the NICE appraisal. ACTIVE will continue to 10-year follow-up.

The trials are summarised in Table 12.

Table 12. Comparison of all the included trials in the report

Study ID	Interventions	% with previous procedures	Duration of symptoms (mean)	Age (mean)	Duration of follow-up	Results
Basad et al 2010	MACI (n=40) vs. MF (n=20) Single surgeon. Defects 4-10cm^2	Not reported	MACI: 2.2. years MF: 2.5 years	MACI: 33 years MF: 37.5 years	2 years	**Failure:** 1 in MF (time NR) **Lysholm score:** improvement at year 1; persisted to year 2 in MACI (52 baseline, 95 1 year and 92 24 months) but declined in MF (55 baseline, 81 1 year, 69 3 years); MACI vs. MF: p=0.005 **Tegner score:** improvement statistically significant from baseline to end of f/u in both groups (p<0.0001). Improvement more in MACI than in MF but not statistically significant (p=.04)
Saris et al 2014 (SUMMIT trial)	MACI (n=72) vs. MF (n=72)	MACI: 90% MF: 84%	MACI: 5.8 years (range 0.5 to 28 years); MF: 3.7 years (range 0.1 to 15.4 years)	MACI: 35 years MF: 33 years	2 years	**Change in KOOS pain score** from baseline to 2 years: MACI 45.5 vs. MF 35.5, p=0.001 **Change in KOOS function score** from baseline to 2 years: MACI 46 vs. MF 36.1, p<0.001 **% of responders:** MACI 87.5% vs. MF 68.1%, p=0.016 **Modified Cincinnati knee score:** greater in MACI than in MF (difference 1.05, p=0.002) **International Knee Documentation Committee (IKDC) score:** MACI 32.8 vs. 29.5 MF, p=0.069 **Failures:** MACI none vs. MF one
Vanlauwe et al 2011 [Saris et al 2008/2009]	CCI (n=57) vs. MF (n=61)	CCI: 88% MF: 77%	CCI: 1.97 years MF: 1.57 years	33.9 years both groups	5 years	At 5 years, **overall KOOS score** and its subdomains: Improved in both treatments, difference 7.10 95% CI -0.52 to 14.73, p=0.068 **Subgroup analysis:** **KOOS score** greater in CCI than in MF in patients with onset of symptoms <3 years (25.96 SE 3.45 vs. 15.28 SE 3.17, p=0.026). Difference not significant in those with onset of symptoms >3 years. **Failure:** CCI 7 patients (13.7%), MF 10 (16.4%) patients Most failures in MF occurred in first 3 years while those in CCI group in the fourth year or later. Failure more common in males than in females (CCI: 6/19 females vs. 1/32 males; MF: 7/20 vs. 3/41)
ACTIVE trial	ACI (n=195) Standard	[redacted]	NR	ACI: [redacted] years Standard	5 years	**Failure:** ACI 39%; standard: 36% by five years

Study ID	Interventions	% with previous procedures	Duration of symptoms (mean)	Age (mean)	Duration of follow-up	Results
	treatment (n=195)	[redacted]		treatment: [redacted] years		**Lysholm score assessed by investigators:** [redacted] at the end of first 4 years but at the fifth year score [redacted] **Lysholm score assessed by patients:** no [redacted] **Cincinnati score:** [redacted] **Mean IKDC knee rating score** [redacted]

Previous repairs

As reported earlier, in case series, previous microfracture appears to reduce the success of ACI. The trials reviewed above do not contribute much evidence on this. Basad did not give details of previous surgery. In TIG/ACT only a few (8/57) of the ACI group had had previous microfracture. In SUMMIT 32% of the MACI® group had had previous repair attempts with microfracture but this appeared to have little effect on response rates (no prior repairs 90% response, more than one, 84%). In ACTIVE almost half had a previous repair procedure but results are not given separately for them. Several factors need to be considered in interpreting the evidence. Firstly, we are somewhat reliant on subgroup analysis. Secondly, those who have had previous surgery may be older than those going straight to ACI, and chondrocyte viability declines with age. Thirdly, some of the older trials had few patients who had not had prior surgery. Lastly, and most importantly, the evidence does not suggest that ACI is not worthwhile after prior microfracture, but only that it is not as successful. Hence there is no reason not to try ACI.

Duration of symptoms

In SUMMIT, responses rates were similar at 2 years – 82% for those with symptoms for less than 3 years, 92% in those with longer durations. Basad did not report results by prior duration but his MACI® patients had a mean duration of symptoms of only 2.2 years. The ACTIVE trial did not report durations. The main evidence comes from the TIG/ACT 5 year data where only those with duration of

symptoms under three years showed a significant difference between ACI and MF. Improvements in KOOS scores at 5 years were 26 for the ACI group versus 15 for the MF group (p = 0.026). For the subgroup with over 3 years' duration, KOOS improvements were 13 for ACI and 17 for MF (NS). This might suggest that ACI is of less value, relative to MF, in patients with longer duration.

Previous studies have shown improvements with ACI after long duration of symptoms. In the trial by Bentley and colleagues[75], most patients receiving ACI had excellent Cincinnati scores results despite a mean duration of symptoms of 7.2 years. In the trial of ACI-C versus MACI by Bartlett and colleagues[54], 59% of the ACI-C group and 72% of the MACI group had good or excellent Cincinnati scores despite duration of symptoms of approximately 10 and 7 years respectively. In another study from Stanmore by Biant and colleagues[76], of a cohort of 104 ACI patients followed for at least 10 years, 66% had excellent or good Cincinnati scores despite an average duration of symptoms before AC of 7.8 years.

ACI-C or MACI?

In a very large cohort of 827 patients with mean duration of follow-up 6.2 years, Nawaz and colleagues[77] reported better results with MACI compared to ACI-P or ACI-C, though this was probably due to different durations, since the ACI groups came from an earlier period and so had more time for knee status to decline. The RCT of ACI-C versus MACI by Bartlett and colleagues[54] found no difference at one year.

In practice, ACI has evolved and most use is now expected to be MACI, with characterised chondrocytes.

Predicting success

Nawaz and colleagues[77] summarised the results from their very large cohort study thus:
Analysis of the influence of individual factors showed that degenerative change and previous procedures played a key negative role in long-term graft survival. Our study suggests that the ''ideal'' candidate for autologous chondrocyte implantation is a younger individual with a single lesion on the trochlea or the lateral femoral condyle, with no previous procedures or evidence of degenerative changes. This ''ideal'' patient group had a survival rate of nearly 80% compared with 50% for the entire cohort at twelve years, with grafts in medial and lateral femoral condyle defects having survival rates of 74% and 87%, respectively, at ten years.

Survival of repairs.

The two-year differences between MF and ACI or MACI arise mainly because symptom scores reach a plateau sooner after MF than after ACI. Saris (2009)[67] reported (from graph) that a KOOS plateau

was reached with MF by 12 to 18 months, whereas improvements continued after ChondroCelect ACI-P. The SUMMIT investigators showed a plateau before 12 months with MF but not till 18 months with MACI®.[97]

In the TIG/ACT trial, Saris et al[67] reported that (from graph, so approximate) that about 7% of MF repairs had failed by 20 months and 11.5% by 36 months (but based on only 7 failures in the MF group). The longer term results reported by Vanlauwe et al[40] showed the plateau in the KOOS score in the MF group from 12 months to 60 months whereas the ChondroCelect group with duration of symptoms < 3 years at surgery, reached a plateau at 36 months. The CC group with >3 year showed no difference from MF with an early plateau and lines almost overlapping.

Basad[61] reported that the Lysholm score in the MF group improved from 55 at baseline to 81 at 12 months but then declined to 69 at 24 months. The MACI group had a baseline score of 55, improving to 95 at 12 months, maintained to 92 at 24 months.

Bhosale and colleagues from Oswestry[116] report results at an average of 5 years (range about 3 to 9 years) amongst 80 patients, all but four having had ACI-P. The median baseline Lysholm score was 54 which improved to a median of 78 at 12 months post-op. Of the 80, 65 improved and scores at 15 months were maintained for up to 9 years. They also reported that higher age, female gender, and larger defect size were associated with greater benefit but none of these associations were statistically significant. They concluded that a good result at 15 months is durable.

5 Chapter 5 – The cost-effectiveness of autologous chondrocyte implantation

5.1 Introduction

The first aim of this analysis is to determine whether autologous chondrocyte implantation (ACI) is cost-effective compared to the current standard treatment of microfracture (MF) as primary treatment for patients with symptomatic articular cartilage defects of the knee. We use ACI as a generic term to cover all relevant forms of ACI.

After the first procedure, patients may have a number of outcomes:

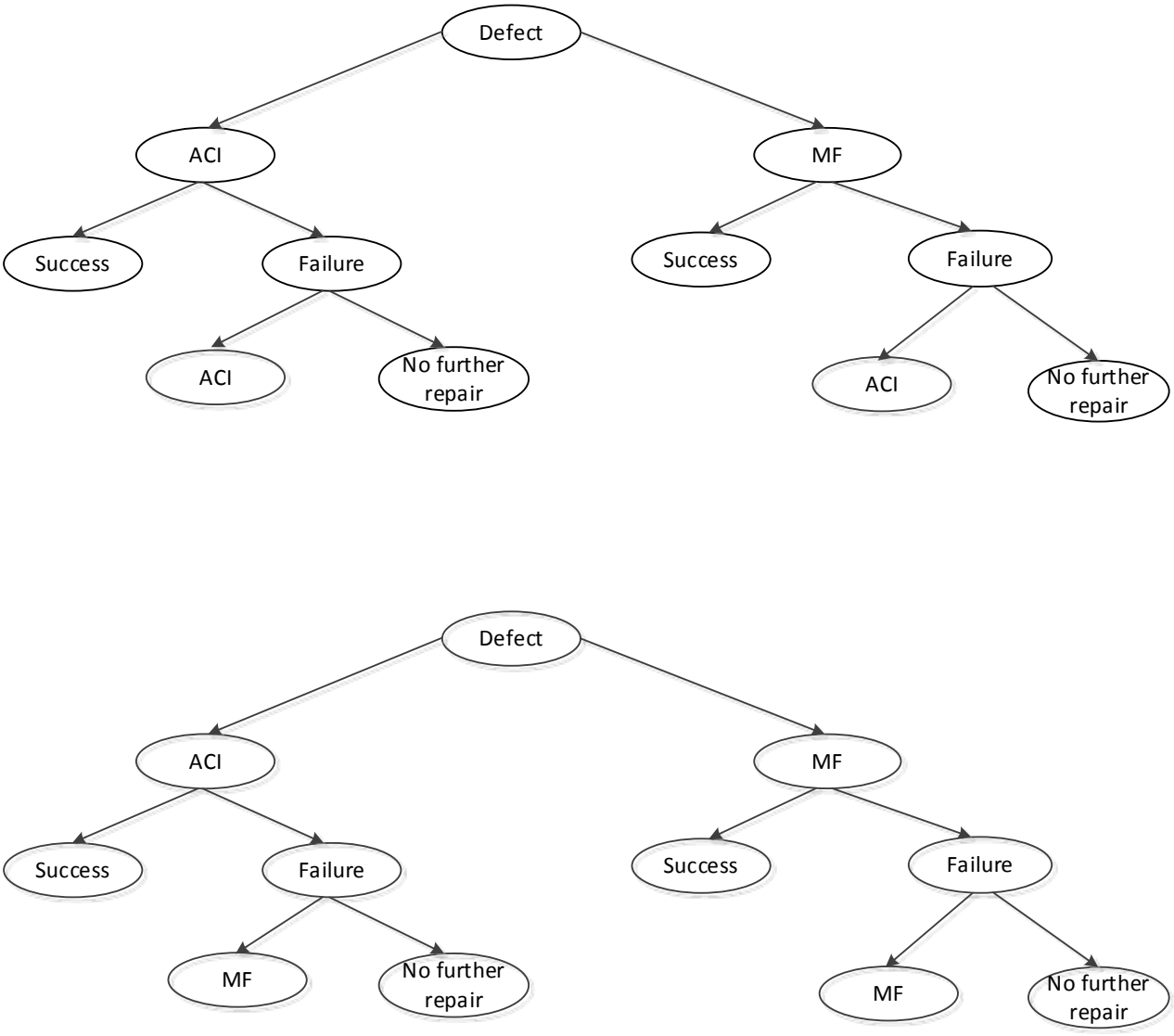
- Permanent success, more likely with ACI than MF;
- Temporary success followed by a second attempt at repair, or at a longer interval, knee replacement;
- Failure followed by another repair;
- Failure, but the patient may decide against another repair and treat symptoms with analgesics, perhaps because they got some relief from the first repair. He/she would probably develop OA, and might have a knee replacement in later life, ideally not till over 55.

Second repairs could be ACI or microfracture.

A simplified diagram of the repair options are shown in Figure 3. The simplifications are two-fold. Firstly, "success" may not be permanent, especially in the case of MF. Secondly, this figure does not show longer term sequelae such as OA and need for knee replacement. This is shown in the detailed model diagram later. We distinguish repairs, ACI and MF, from replacements such as partial or total knee arthroplasties (PKR and TKR).

In Figure 3, scenario 1 (top) shows that all second repairs are ACI and scenario 2 (bottom) shows all second repairs are MF. This is to allow a direct comparison between ACI and MF as first procedure. In practice if a second repair is needed, the choice may vary according to what the first repair was – we deal with other possible sequences later.

Figure 3. Patient pathways for ACI or MF – scenario 1 (above), scenario 2 (below)



This chapter describes the structure of the model, the parameters used within the model (transition probabilities, resource use, costs and utilities), the assumptions made, the different scenarios which have been evaluated, the base-case results and the sensitivity analyses undertaken.

5.2 Model structure

A Markov (state-transition) model was developed in Microsoft Excel. A Markov model was considered the most appropriate as we wanted to determine whether ACI would postpone or avoid knee replacement in the longer term. The economic model reflects the different clinical pathways for patients with symptomatic articular cartilage defects of the knee. We have used information from the systematic review of cost-effectiveness studies for ACI: most notably Clar et al[3] and Gerlier et al[102]

and this has been supplemented by information from expert clinical opinion in order to develop the clinical pathways.

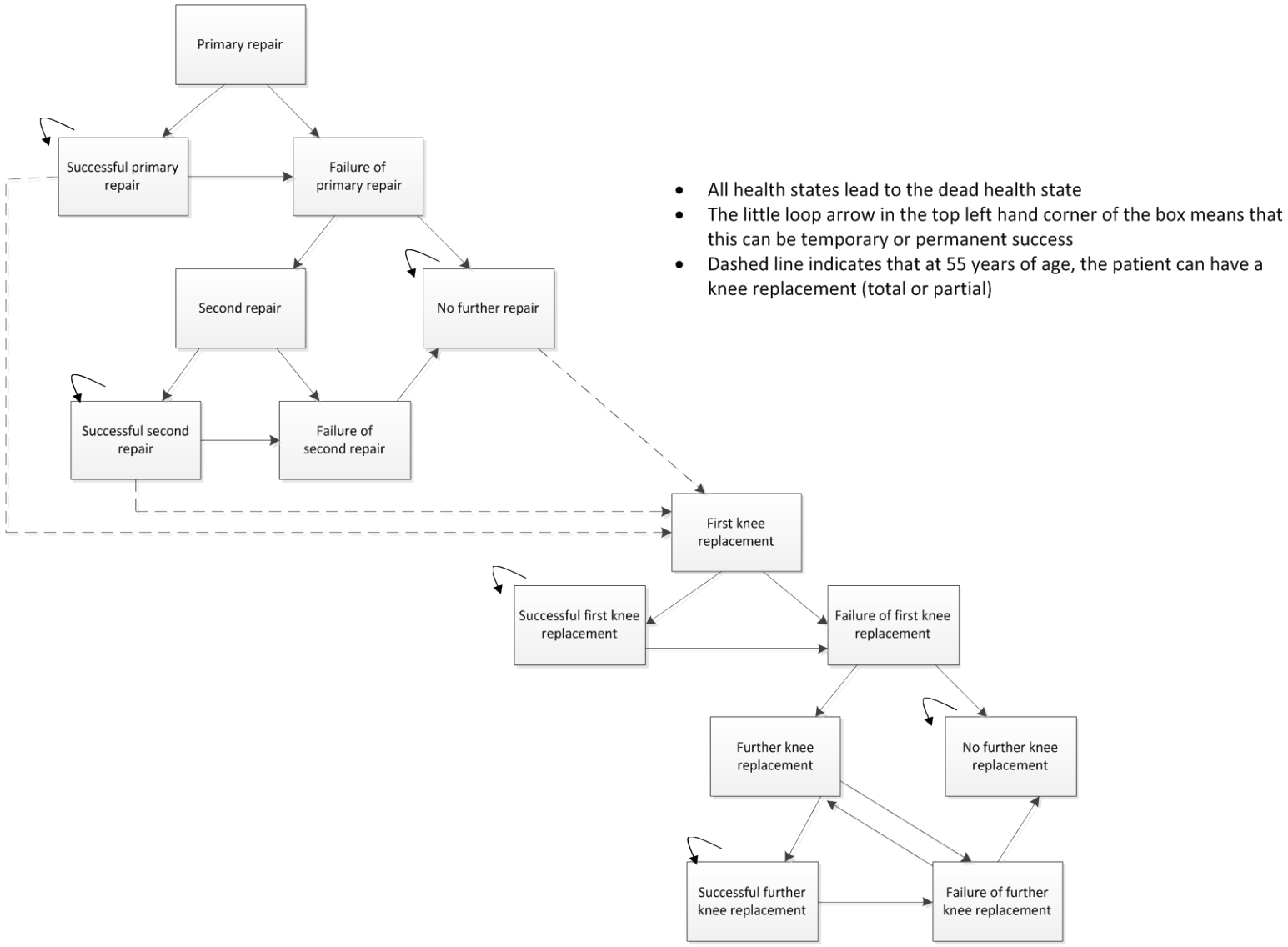
In practice, some patients who would be considered for ACI should that be approved, will have had a previous procedure, most often microfracture, but this is covered in the set of sequences below. For those who do need a second repair, we considered both ACI and MF in the sequences within the model. We have assumed that patients will have a maximum of two repairs and combinations could be as follows:

1. ACI (ACI): patients receive ACI as a primary repair and **if** they require a second repair this will also be an ACI.
2. MF (MF): patients receive MF as a primary repair and **if** they require a second repair this will also be a MF.
3. ACI (MF): patients receive ACI as a primary repair and **if** they require a second repair this will be a MF.
4. MF (ACI): patients receive MF as a primary repair and **if** they require a second repair this will be an ACI.

Clinical pathways

Figure 4 shows the detailed clinical pathway for people receiving treatment for symptomatic articular cartilage defects of the knee.

Figure 4. Clinical pathways for patients with articular cartilage defects of the knee joint



Knee repairs

The starting point for the model is the primary repair which could either be ACI or microfracture. After the primary repairs, patients can then either move to the successful primary repair health state or to the failure of primary repair health state. Successful can be permanent - the first repair works and they do not require a second repair. So they can stay in the successful primary repair health state until they die. Or success can be temporary (the patient has no symptoms for years but after a while the repair fails), so the patient then moves to the failure of primary repair health state. They can then have a second repair, or they can either choose not to have another repair (no further repair health state), and rely on analgesics to relieve symptoms – that is, the patient chooses to accept the pain and treat it rather than have another attempt at repair, though later he/she may have a knee replacement.

The second repair could be either ACI or microfracture. Based on clinical opinion, we have assumed that patients will have a maximum of two repairs. Once the patient has had a second repair they can then either move to the successful second repair health state or to the failure of second repair health state. The successful second repair can be permanent (similar to the successful primary repair), and patients stay in this health state until they die. Or it could be a temporary success, so then the patient later moves to the failure of second repair health state. We are assuming that patients whose second repair fails do not have another repair and they move to the no further repair health state.

Patients who move to the no further repair health state after failure of repair, can choose not to have another repair procedure and accept the pain, taking analgesics as required (that is, they can stay in this health state), until they reach the knee replacement age range, when their options are knee replacement or continued symptomatic treatment. Those who choose not to have a further repair may have had partial relief from symptoms, so we rate their utility as better than the baseline one.

Knee replacements

We assume for simplicity that patients over the age of 55 cannot have an ACI, but only have a knee replacement or symptomatic care. This is line with the MSAC report which indicated that MACI/ACI was not indicated for patients older than 55 years.[30] The first knee replacement can be either a partial (unicompartmental) knee replacement (PKR) or total knee replacement (TKR). According to statistics from the National Joint Registry, the average ages of patients having a PKR and TKR are 64 and 70 years of age, respectively.[117] However, we know that patients being considered for ACI are a lot younger than the general population (average age early thirties), so that if the repair fails, they are more likely to have a knee replacement at an earlier age. In line with expert clinical advice, we are assuming that patients can have one or more knee replacements. The first may succeed for life. If not, they can have another replacement, or choose not to have another replacement. The first knee

replacement could either be PKR or a TKR, but we have assumed that all subsequent replacements will be TKRs.

A patient can move to first knee replacement from either a temporarily successful primary repair health state, a temporarily successful second repair health state or from the no further repair health state when they reach the knee replacement age range. The first knee replacement can be a success, so the patient moves to the successful first knee replacement health state, or the replacement can fail over time, so they move to the failure of first knee replacement health state. The first knee replacement can be a permanent success until they die, or a temporary success because the knee replacement fails over time, so they move to the failure of first knee replacement health state, from which patients can choose to have another knee replacement or to have no further knee replacement (so move to the no further knee replacement health state).

The second knee replacement can be a permanent success (till death) or it could be a temporary success, and patients move to the failure of further knee replacement health state, from which they can choose to have no further knee replacement (but use symptomatic treatment) and or to have another (3^{rd}) knee replacement. Based on clinical opinion, we have assumed that patients can have more than two knee replacements. Patients who move to the no further knee replacement health state, choose not to have another knee replacement and stay in this health state until they die.

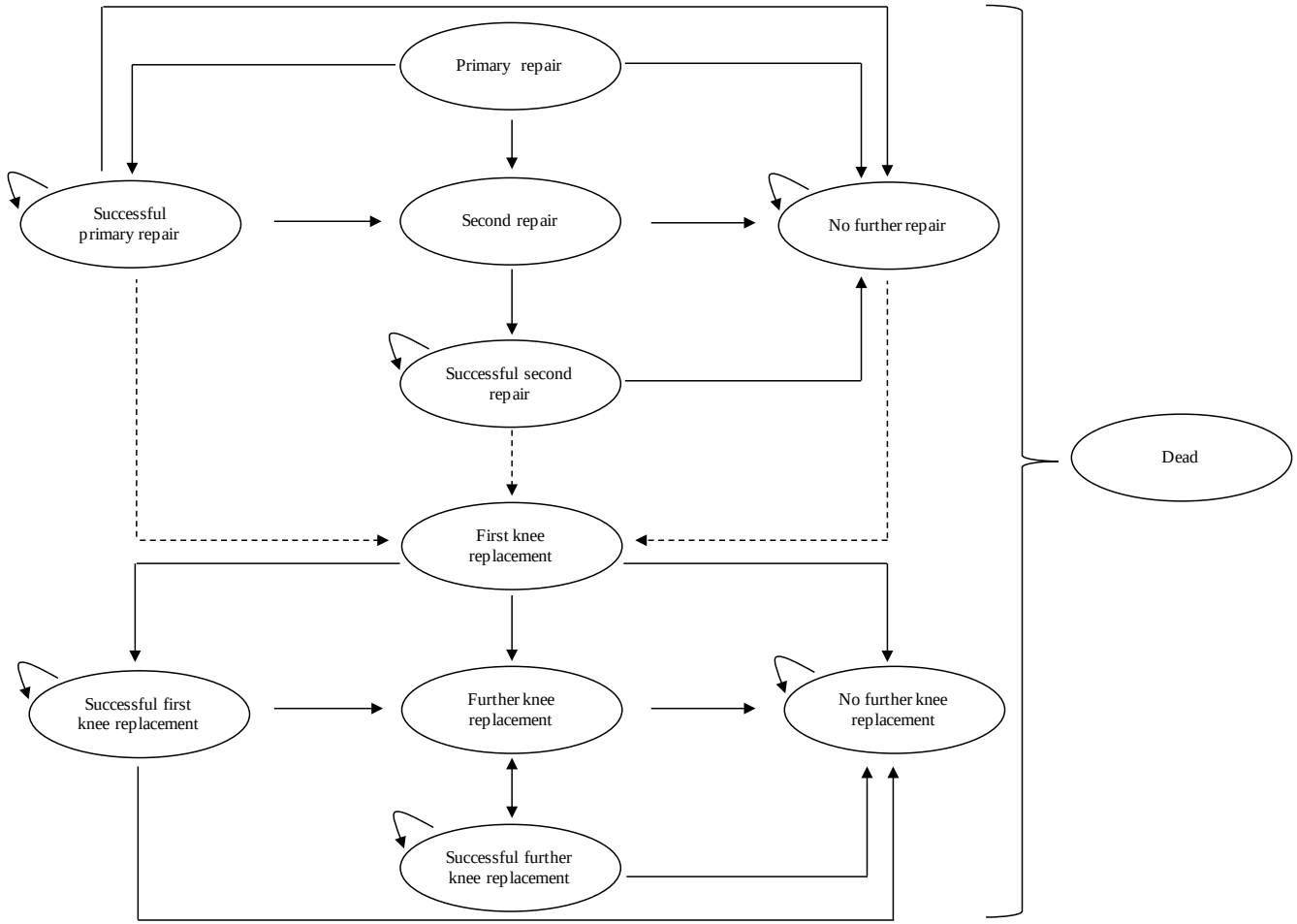
Deaths

Patients can move to death from any of the repair and replacement health states due to all-cause mortality, or because of the rare mortality associated with PKR or TKR (such as deep vein thrombosis and pulmonary embolism). The latter becomes more relevant in later stages because replacing previous knee replacements requires more extensive procedures.

Markov model structure

The Markov model structure is shown in Figure 5. In line with the clinical pathway shown in Figure 4, the model shows the different health states and events which can take place. The different events health states for the model are shown by the ovals. The model shows all the transitions that can happen between the different health states by the direction of the arrows. The little loop arrows in the left hand corner of the ovals (recurring arrow) means that a patient can stay in that health state for more than one cycle, and perhaps indefinitely (until they die). The dashed line indicates that at 55 years of age, the patient can choose to have a knee replacement (total or partial). Transition probabilities i.e. the rate of progression from one health state to another (or for staying in the same health state) were identified from the literature.

Figure 5. Markov model structure for patients with articular cartilage defects of the knee joint



Base-case analysis

Many people with cartilage injury are young and involved in sports, and this is where most of the injuries occur. We have not differentiated by gender as evidence shows that there is no difference in the success or failure of the two different procedures (ACI and MF) if lesions are comparable.[106] For the base-case analysis, we have adopted a lifetime horizon (i.e. patients can live to 100 years) with a cycle length for the model set at one year and transitions between each health state occurring at the end of each cycle. A cycle length of one year is reasonable, given the time it takes patients to recover from surgery. A hypothetical cohort of a 1,000 patients with symptomatic articular cartilage defects of the knee with a starting age of 33 years is followed from their first repair. The analysis is conducted from the perspective of the NHS and personal social services (PSS). All costs are in pounds sterling (£) in 2012/2013 prices. Health outcomes were measured in quality-adjusted life years (QALYs). Results are expressed as incremental cost per QALY gained. An annual discount rate of 3.5% is applied to both costs and outcomes.

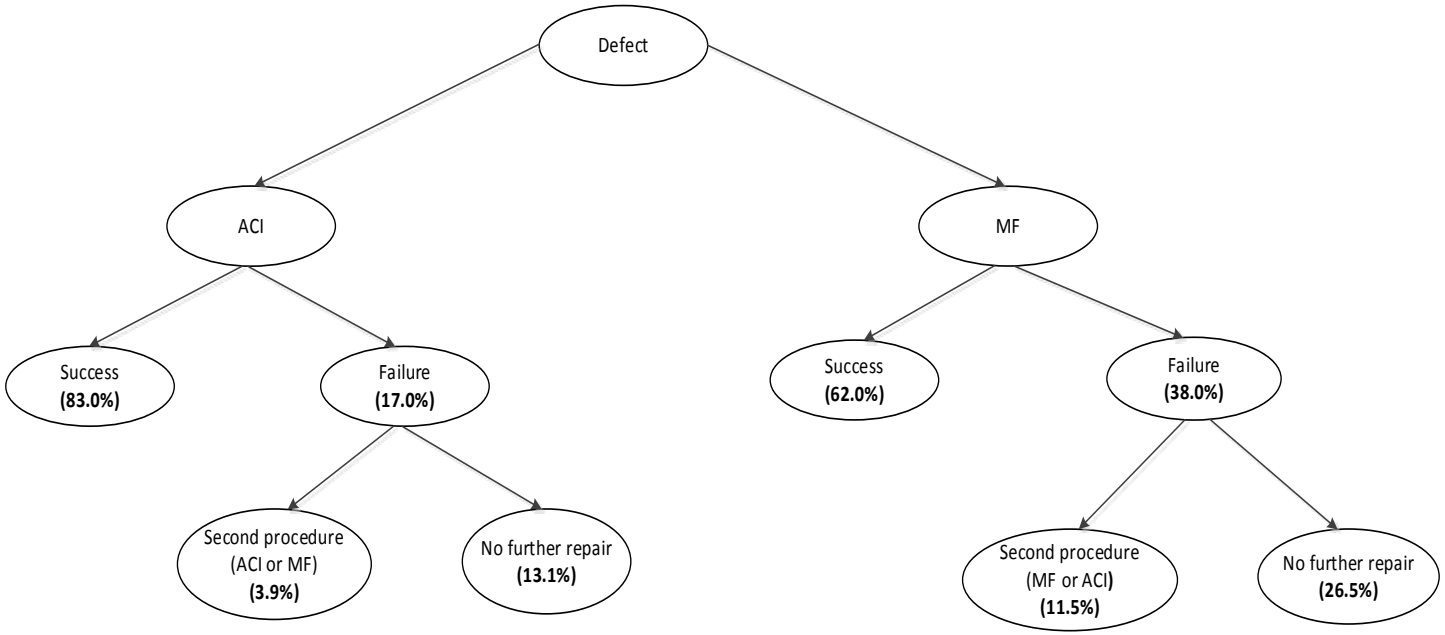
5.3 Model inputs

5.3.1 Transition probabilities

For the base-case analysis, annual transition probabilities were based on data derived from the literature and in consultation with clinical experts. For the primary and second repairs, for both ACI and microfracture these transition probabilities were based on success rates for ACI compared with MF, and these probabilities came from two main studies: Saris et al[67] and Saris et al[97]

Figure 6 shows a flowchart with the proportion of people achieving success or failure with each repair. The timing of knee replacement after one of the repair health states was based on data from the RCT of ACI and MF by Knutsen et al[64]. Transition probabilities for success and failure for patients who needed knee replacements or knee replacement revisions were derived from two studies: Gerlier et al[102] and Dong and Buxton.[118] Appendix XI details the literature used and the assumptions made for deriving these probabilities and Table 34, Table 35 and Table 36 show the transition probabilities which have been used in the base-case analysis.

Figure 6. Proportion of patients achieving success/failure with ACI or MF at 36 months



5.3.2 Utilities

There are very few studies reporting health state utility values for patients with symptomatic articular cartilage defects of the knee. The main studies reporting utility values have been summarised in Chapter 3. (Clar et al[3], Derrett et al[101], and Gerlier et al[102]) In the previous HTA report, the pre-operative quality of life value was taken to be 0.80 and for those that had successful knee repair there was a utility gain of 0.10 (utility score for successful knee repair was 0.90) and for those where the knee repair failed the utility value remained at the pre-operative value (utility score for knee repair failure was 0.80). (Clar et al[3]) Derrett and colleagues used the EQ-5D-3L to elicit utility scores and the ACI waiting list group had a pre-surgery utility score of 0.41. After surgery, the EQ-5D-3L mean score for the ACI group was 0.64 and for mosaicplasty was 0.47, a utility gain of 0.23 and 0.06, respectively.

For our model we have used utility values for knee repairs from the study by Gerlier et al who compared ACI with MF using data from the TIG/ACT ChondroCelect trial. They 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 RCT 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. We used two other studies to supplement utility values for knee replacement. The first study is by Dong and Buxton[118] who developed a Markov model to compare the cost-effectiveness of TKR using computer assisted surgery with that of TKR using a conventional manual method in the absence of formal clinical trial evidence. The second study is by Jansson and Granath[119] who analysed EQ-5D data before and after knee arthroplasty.

Table 13 shows the base-case mean utility values used in the model. For the repairs these values were all obtained from the paper by Gerlier and colleagues who used the SF-36 and the KOOS measures to estimate utility scores. The mean utility value for patients before they have a primary repair (before ACI or MF) was 0.654 – this utility value was based on the initial value before the intervention. For those patients who had an ACI as a first repair and moved to the successful primary repair health state, we assumed that the patients mean utility value after surgery for the first year would be 0.760 (this value was based on year one post-intervention regardless of the outcome and takes into account the long-rehab period and abstinence from active pursuits) [Gerlier et al, 2010], and if they remain in this health state in subsequent years, their utility value would remain constant at 0.817. This latter value was based on patients who had clinical success for five years after the intervention [Gerlier et al, 2010]. For those patients who had an MF as a first repair and moved to the successful primary repair health state, we assumed that the patients mean utility value after surgery for the first year

would be 0.760 (this value was based on year one post-intervention regardless of the outcome) [Gerlier et al, 2010]. For years two to four after MF this mean utility value would increase to 0.817. This reflects the quite long rehabilitation required in the first year after the procedures, and the time taken for the cartilage to be replaced. For years 5 and onwards for patients who stay in this same health state, we have assumed that utility would fall to the same as pre-surgery (mean utility value is 0.654 [redacted]

For those patients who require a second repair, the mean utility value was 0.654 – this value was based on the utility value before the intervention [Gerlier et al, 2010]. For those requiring a second repair there are four possible sequences: ACI (ACI), ACI (MF), MF (ACI) and MF (MF). Utilities for patients having a second successful ACI after the first ACI were assumed to be the same as those who had a successful ACI as a first repair. Utilities for patients having a successful MF after an initial ACI that failed were assumed to be the same as those who had a successful MF as a first repair and moved to the successful primary repair health state.

Patients who have a successful ACI after an initial MF move to the successful second repair health state. However, as noted in Chapter 2, ACI is less effective in patients who have had prior MF, so for years 4 and 5 we have used the average of two utility values from Gerlier et al (2010): based on year 1 post-intervention (utility value = 0.760) and clinical success after five years after the intervention (utility value = 0.817) – so the mean utility value for ACI after MF was 0.789. Utilities for patients having a successful second MF after a failed initial MF and who moved to the successful second repair health state were assumed to be the same as those who had a successful MF as a first repair.

For patients who moved to the no further repair health state the mean utility value was 0.691 – this value was based on patients who had not a successful result five years after surgery [Gerlier et al, 2010] but we have assumed that those who choose to have no further repair may have had some benefit from the first repair, and so do not go back as far as the original baseline utility.

Mean utility values are the same for knee replacements after ACI or MF. Before the first knee replacement procedure, patients who received a TKR and PKR are assumed to have the same utility value = 0.615. This value was based on an average of two utility values: 1) the EQ-5D index score at baseline pre-operatively for knee arthroplasty (value = 0.51) [Jansson and Granath, 2011] and 2) an estimated value for TKR operation for knee problem (value = 0.72) [Dong and Buxton, 2006]. For patients who move to the successful first knee replacement health state (TKR or PKR), a utility value of 0.780 was also obtained from Dong and Buxton (2006). This utility value was estimated from the generic Knee Society Score scale and was applied to the Markov health state for normal health after

primary TKR. We have also assumed that if patients move to the successful further TKR health state they will have the same utility value as if it was a first TKR. For those patients for whom TKR has failed and need a further TKR, the utility value was 0.557 based on the failed TKR/revision health state from Gerlier et al (2010). Finally, for those patients who move to the no further replacement health state this value (mean = 0.691) was also from Gerlier et al (2010) and was based on patients who had no clinical success five years after surgery (in line with patients who move to the no further repair health state).

Table 13. Base-case mean utility values used in the 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)

* Some patients decide not to have another repair attempt after unsuccessful first repair. We have assumed that they had some benefit and do not go back to their baseline utility.

5.3.3 Resource use and costs

Costs for the different procedures (ACI, MF, PKR/TKR, TKR revisions) and for outpatient visits and rehabilitation are shown in Table 14. We have used national reference costs where possible [NHS references costs, 2013[113]] supplemented by the previous HTA report on cartilage defects in knee joints [Clar et al, 2005]. All unit costs are presented in pounds sterling (£) in 2012/13 prices.

Table 14. Base-case mean costs in £ sterling used in the economic model

Procedure	Information	Unit cost (£)	Source
ChondroCelect and MACI	Product including courier services and development of cell culture	16,000	UK price for ChondroCelect
	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) includes the costs associated with cell development, including the ACI kit, staff time and transporting the cells to and from the laboratory. ACI involves two procedures, the arthroscopic cell harvest and the re-implantation during arthrotomy. We assumed both would be done as day cases. Based on consultation with clinical experts, we have also included the costs of six outpatient visits and three rehabilitation visits in the first year (see Table 15).

The cost of MF procedure (including an inpatient stay) was obtained from Clar et al (2005) and the cost has been updated to 2012/2013 prices using the Hospital and Community Health Services (HCHS) index [Curtis, 2013[114]]. The inpatient stay is required because unlike after ACI, the patients can have considerable pain after MF because of the drilling into bone. Over the course of the year, the patient would also have three outpatient visits and three rehabilitation visits and these costs have been added for this health state (based on information from the clinical experts –Table 15).

The cost for a first knee replacement was obtained from the NHS reference costs [NHS reference costs, 2013[113]]; and we have assumed that it could be either a total knee replacement or a partial knee

replacement. After a TKR, a subsequent TKR is almost double the cost, because it is technically more difficult [Clar et al, 2005]. After a partial knee replacement, a second knee replacement would be a TKR, and we have assumed that this would cost £5,676. If they required any more subsequent knee replacements (all of which would be TKRs) then these would cost £12,959. Based on consultation with clinical experts, in the first year after KR, we have included the cost of two outpatient visits (see Table 15).

Resource use information including inpatient stays, outpatient visits and rehabilitation visits for each of the three procedures were based on expert clinical opinion and are shown in Table 15. Unit costs were obtained from the NHS reference costs (see Table 14) [NHS reference costs, 2013[113]].

Table 15. 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

[#] The cost of inpatient stay has been included in the cost for the different procedures

We have assumed that there will be no further costs after year 1 once patients enter the successful health states (successful primary repair, successful second repair, successful first knee replacement, and successful further knee replacement), as patients incur costs such as outpatient or rehabilitation visits during the first year of either a knee repair or a knee replacement. In addition, for the no further repair health state or the no further knee replacement health state, we have not added any costs for the analgesics based on advice from our clinical experts, as these costs are negligible and these patients are not followed up routinely and it is up to the GP to refer the patient back to the hospital for a knee repair or a knee replacement.

5.3.4 Complications

Adverse events have not been included as there were no important differences between the two treatment arms.

5.3.5 Mortality

Age-specific mortality rates used in the economic model were based on the UK general population lifetime tables from the Office of National Statistics (ONS) [ONS, 2014[120]]. Using the ONS data, the average probability of death for men and women were combined. As the cohort ages, mortality rates generally increase throughout the time horizon in the model. On this basis, in the model patients from any health state can move to the dead health state. Patients undergoing a knee replacement are subject

to a mortality risk during surgery. To reflect this higher mortality, rates were obtained from a study by Mahomed et al[110] as reported in Gerlier et al.[102] For those patients undergoing a TKR and a TKR revision, the mortality rates were reported as 0.7% and 1.1% respectively.[110]

5.4 Measuring cost-effectiveness

The base-case analysis assessed the cost-effectiveness of ACI compared with MF. We calculated for a cohort of patients the expected quality-adjusted survival based on their likelihood of surviving each cycle, their expected health state utility value, and their expected costs. We have adopted a lifetime horizon from a starting age of 33 years. The analysis is conducted from the perspective of the UK NHS and personal social services (PSS). Costs are expressed in 2012-2013 pounds sterling. The main outcome of interest was the quality-adjusted life year (QALY). The different sequences of procedures were ranked in order of increasing cost. We eliminated any categories for which another category was cheaper and more effective (simple dominance). If there was a linear combination of two other categories which were more costly and less effective, these were eliminated (extended dominance). For the remaining options, we reported the incremental cost-effectiveness ratios (ICERs), measured as cost per QALY gained. Discount rates of 3.5% were applied to both future costs and benefits, as costs and benefits accrued in the future are valued less than those accrued today.

Sensitivity analysis assesses the uncertainty in parameter inputs used in the Markov model and to check whether the results obtained are robust. We present both deterministic and probabilistic results. For the deterministic analysis, we identified the key factors driving the cost-effectiveness. For the probabilistic sensitivity analysis (PSA), to reflect the amount and pattern of the variation, the analysis attributes probability distributions randomly around specified parameters with simulations, which are repeated to generate ICERs. The PSA was undertaken using 1,000 simulations. We used the gamma distribution for costs and the beta distribution for utility values and transition probabilities.[121] As the values for costs, utilities and transition probabilities used in the model were means or weighted averages an assumption was made for the standard error in order to calculate the alpha and beta values which are required for the PSA. For example, we have assumed the standard error to be 0.1 of the mean value [Fox et al[122]; Drummond et al,[123]]. These bootstrapped simulations obtained from the PSA were used to construct cost-effectiveness acceptability curves (CEACs), to illustrate the effect of sampling uncertainty, in which individual model parameters were sampled from the appropriate probability distribution. CEACs were presented to indicate the probability of a procedure being cost-effective using a willingness to pay threshold from £0 to £60,000.

5.5 Scenario and sensitivity analyses

Several scenario and sensitivity analyses were conducted by altering base-case inputs to the model.

SA1. In the base-case analysis, the cost of cells for ChondroCelect and MACI procedures were £16,000. We are aware that confidential discounts are provided to the NHS by manufacturers. So in the sensitivity analysis we have varied this figure by reducing the costs by 25%, 50% and 75% - so that the cost of cells are £12,000, £8,000 and £4,000 respectively. Note that the cost of cell production in Oswestry is £4,125 per patient.

SA2. In the base-case analysis, a lifetime horizon was chosen with the starting age of 33 years for the cohort. In the sensitivity analysis we have varied the time horizon (10, 20, 30, 40 and 50 years) to see how this affects the incremental cost-effectiveness ratio.

SA3. In the base-case analysis, according to clinical advice we costed MF as an inpatient procedure (£3,020). However, we know that sometimes this procedure is done as day case. In the sensitivity analysis we have assumed that MF is done as a day case procedure and the associated cost is £1,034.

SA4. In the base-case analysis, the success rates for MF were based on existing evidence. However, there are new types of MF procedures and these could have better success rates. We have no evidence for this, but in a 'what if' sensitivity analysis we have checked what would happen to ICERs if the success rates for MF could increase by 20% and 40%. The effect are to increase duration of benefit after MF.

SA5. In the base-case analysis the starting age for the cohort was 33 years. In the sensitivity analysis the starting age is changed to 45 years (patients are nearer to the knee replacement age) to see how this affects the incremental cost-effectiveness ratio.

SA6. In the base-case analysis we used utility values from the paper by Gerlier et al[102] who compared ACI with MF. In this sensitivity analysis we have used utility values which are from the ACTIVE trial (Oswestry submission).

5.6 Results

We present here the cost-effectiveness deterministic and probabilistic results for ACI compared with MF.

5.6.1 Base-case cost-effectiveness results

1,000 patients entered the model with a starting age of 33 years. For the primary repair these patients can receive either an ACI or MF, and if these patients require a second repair it could either be an ACI or MF. Many will not require a second repair, but the cost-effectiveness of the primary repair depends partly on the costs of subsequent interventions required or avoided so we need to consider the sequence options.

Table 16 shows the base-case deterministic and probabilistic cost-effectiveness results for the lifetime horizon for the two different scenarios. For scenario 1, if patients required a second repair this would be an ACI and for scenario 2 if patients required a second repair this would be MF (see Figure 3). After MF, 11.9% of patients required a second procedure and after ACI, 3.9% of patients required a second repair. Looking at the discounted deterministic results, for scenario 1, ACI cost £14,524 more than MF, but generated more 1.6273 more QALYs than MF. The cost per QALY gained for ACI compared with MF was £8,925. For scenario 2, ACI again was more costly (incremental cost = £14,921) but generated more QALYs (1.5245) and the resulting cost per QALY gained was £9,788. For both scenarios, ACI as a first repair was more cost-effective than MF as a first repair. These results were of similar magnitudes and directions for both the undiscounted deterministic results and the probabilistic results.

Table 16. Base-case deterministic and probabilistic cost-effectiveness results (by scenario)

Procedure	Total mean costs £	Total mean QALYs	Incremental costs £	Incremental QALYs	ICER £ (cost per QALY gained)
Deterministic - undiscounted					
Scenario 1					
MF (ACI)	8,028	34.1648	-	-	-
ACI (ACI)	22,252	35.7922	14,524	1.6273	8,925
Scenario 2					
MF (MF)	6,234	34.1259	-	-	-
ACI (MF)	21,155	35.6504	14,921	1.5245	9,788
Deterministic - discounted					
Scenario 1					
MF (ACI)	6,607	17.0284	-	-	-
ACI (ACI)	20,921	18.0228	14,314	0.9944	14,395
Scenario 2					
MF (MF)	5,015	17.0033	-	-	-
ACI (MF)	19,892	17.9570	14,877	0.9537	15,598
Probabilistic - discounted					
Scenario 1					

MF (ACI)	6,624	16.9878	-	-	-
ACI (ACI)	20,838	18.0343	14,214	1.0466	13,581
Scenario 2					
MF (MF)	5,030	16.9654	-	-	-
ACI (MF)	19,809	17.9490	14,779	0.9836	15,026

One of the key cost drivers was the cost of the cells for the ACI procedure, 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 (in which the utility is lower).

Figure 7 presents the cost-effectiveness acceptability curves for the base-case results for scenarios 1 and 2, respectively. For scenario 1, if the decision maker was willing to pay £14,000, the probability that both ACI and MF were cost-effective was approximately 50%; however, if the decision maker was willing to pay £20,000, ACI was probably 59% more likely to be cost-effective than MF (see Figure 7a). These results were similar for scenario 2, if the decision maker was willing to pay £20,000, the probability that ACI was more cost-effective than MF was 56% (see Figure 7b).

Figure 7. a) Cost-effectiveness acceptability curve - base case results: scenario 1; b) Cost-effectiveness acceptability curve - base case results: scenario 2

Table 17 shows the base-case deterministic and probabilistic cost-effectiveness results for the lifetime horizon, ranked by the least costly sequence (option). For the discounted deterministic results MF (MF) was the least costly option and had the fewest QALYs, whereas ACI (ACI) was the most expensive option but generated more QALYs. The incremental cost-effectiveness ratio between the two initial MF options: MF (ACI) vs MF (MF) was nearly £63,500; this is because doing ACI after MF is less successful for reasons explained in Chapter 2. The ICER between ACI (MF) and MF (ACI) was just over £14,000; doing ACI first is more cost-effective. The ICER between the two initial ACI options: ACI (ACI) vs ACI (MF) was just under £16,000; even if the first ACI fails, there is good enough chance of a second ACI succeeding to make the ICER for a repeat ACI quite reasonable. So initial ACI appears more cost-effective than initial MF and for those that need a

second repair after the first ACI, this should be another ACI. These results were of similar magnitudes and directions for the probabilistic results and also for the undiscounted deterministic results.

Table 17. Base-case deterministic and probabilistic cost-effectiveness results

Procedure	Total mean costs £	Total mean QALYs	Comparison	Incremental costs £	Incremental QALYs	ICER £ (cost per QALY gained)
Deterministic - undiscounted						
MF (MF)	6,234	34.1259	-	-	-	-
MF (ACI)	8,028	34.1648	MF (ACI) v MF (MF)	1,795	0.0389	46,111
ACI (MF)	21,155	35.6504	ACI (MF) v MF (ACI)	13,127	1.4856	8,836
ACI (ACI)	22,252	35.7922	ACI (ACI) v ACI (MF)	1,397	0.1418	9,856
Deterministic - discounted						
MF (MF)	5,015	17.0033	-	-	-	-
MF (ACI)	6,607	17.0284	MF (ACI) v MF (MF)	1,592	0.0251*	63,450
ACI (MF)	19,892	17.9570	ACI (MF) v MF (ACI)	13,285	0.9287	14,306
ACI (ACI)	20,921	18.0228	ACI (ACI) v ACI (MF)	1,029	0.0658	15,648
Probabilistic - discounted						
MF (MF)	5,030	16.9654	-	-	-	-
MF (ACI)	6,624	16.9878	MF (ACI) v MF (MF)	1,595	0.0223*	71,476
ACI (MF)	19,809	17.9490	ACI (MF) v MF (ACI)	13,185	0.9613	13,716
ACI (ACI)	20,838	18.0343	ACI (ACI) v ACI (MF)	1,029	0.0853	12,059

* As the incremental QALYs are near zero, the ICER can fluctuate widely

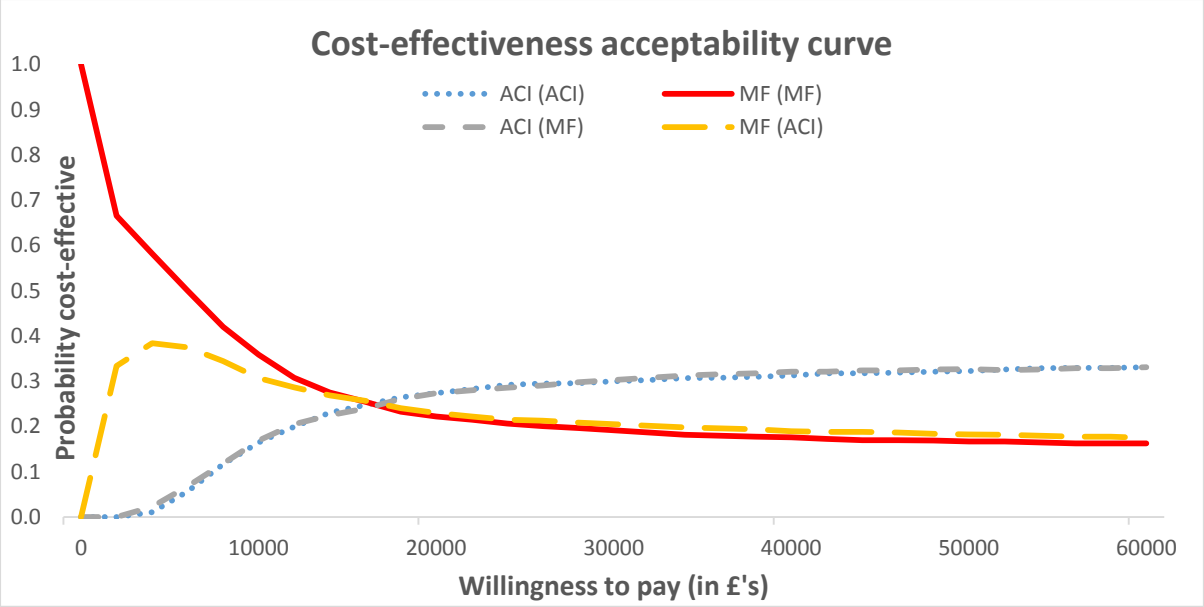


Figure 8. Cost-effectiveness acceptability curve – base-case results: all sequences

Figure 8 presents the cost-effectiveness acceptability curve for the base-case results for all sequences. The graph shows that for amounts below £14,000 then MF (MF) appears cost-effective compared to the other three options. At a willingness to pay of £16,000, there is not much difference between the four options. However, if the decision maker is willing to pay £18,000 or more for a QALY, than ACI as a first procedure (either ACI (ACI) or ACI (MF)) is probably more cost-effective than MF (either MF (ACI) or MF (MF)) as a first procedure.

5.6.2 Scenario and sensitivity analysis cost-effectiveness results

This section highlights the results from the different sensitivity analyses which were undertaken.

a) SA 1. Cell cost reduction

In the base-case analysis, the cost of cells for ChondroCelect and MACI procedures was taken to be £16,000. We know that there are confidential discounts provided to the NHS by manufacturers. In this sensitivity analysis we have varied this figure by reducing the cell costs by 25% (£12,000), 50% (£8,000) and 75% (£4,000). The last figure may seem very low but it is similar to the cost provided in the Oswestry submission, for cells produced in an NHS facility.

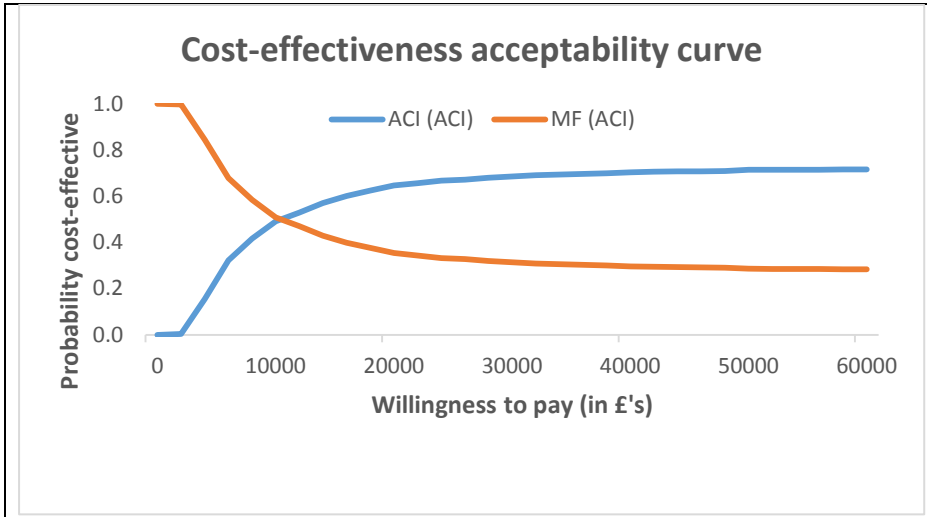
Table 18 shows the results when the cost of cells is reduced. When there was a reduction in cell costs (for all three cost reductions), even though ACI was more costly than MF, there were more QALYs gained with ACI than MF. For a 25% cell cost reduction, the deterministic cost per QALY gain ratio for ACI compared with MF was £10,523 for scenario 1 and £11,404 for scenario 2. The cost per QALY gain ratio for a 50% cell cost reduction for ACI compared with MF was £6,651 (scenario 1) and £7,210 (scenario 2) and the resulting figures for a 75% reduction was £2,779 (scenario 1) and £3,016 (scenario 2). With the reduction in cell costs, the cost-effectiveness of ACI improved relative to MF. Hence, the cost of cells was a key driver for the cost-effectiveness. These results were of similar magnitudes and directions for the probabilistic results.

Table 18. Sensitivity cost-effectiveness results (by scenario) – cell cost reduction

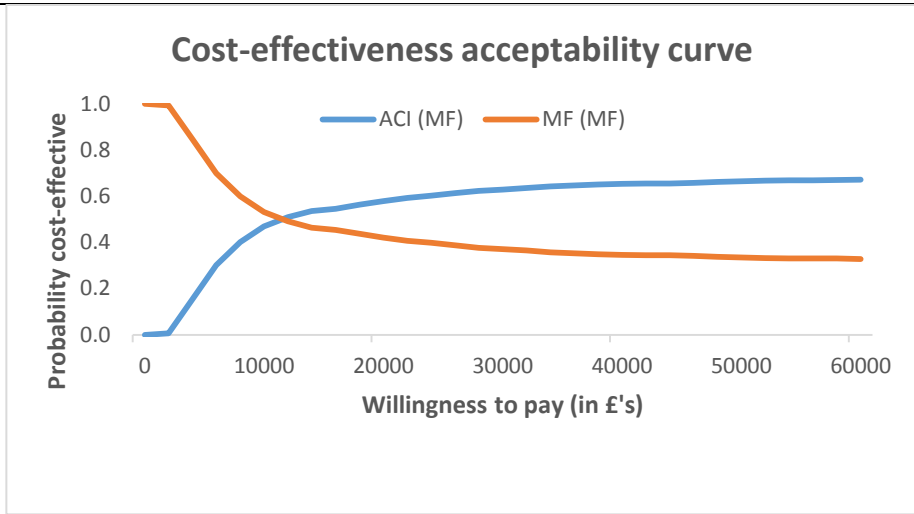
Procedure	Total mean costs £	Total mean QALYs	Incremental costs £	Incremental QALYs	ICER £ (cost per QALY gained)
Deterministic – 25% reduction					
Scenario 1					
MF (ACI)	6,183	17.0284	-	-	-
ACI (ACI)	16,647	18.0228	10,464	0.9944	10,523
Scenario 2					
MF (MF)	5,015	17.0033	-	-	-
ACI (MF)	15,892	17.9570	10,877	0.9537	11,404
Probabilistic – 25% reduction					
Scenario 1					
MF (ACI)	6,183	17.0305	-	-	-
ACI (ACI)	16,637	18.0497	10,454	1.0192	10,258
Scenario 2					
MF (MF)	5,009	17.0086	-	-	-
ACI (MF)	15,880	17.9502	10,871	0.9416	11,545
Deterministic – 50% reduction					
Scenario 1					
MF (ACI)	5,760	17.0284	-	-	-
ACI (ACI)	12,373	18.0228	6,614	0.9944	6,651
Scenario 2					

MF (MF)	5,015	17.0033	-	-	-
ACI (MF)	11,892	17.9570	6,877	0.9537	7,210
Probabilistic – 50% reduction					
Scenario 1					
MF (ACI)	5,770	17.0250	-	-	-
ACI (ACI)	12,362	18.0100	6,592	0.9850	6,693
Scenario 2					
MF (MF)	5,020	16.9907	-	-	-
ACI (MF)	11,876	17.9123	6,856	0.9216	7,439
Deterministic – 75% reduction					
Scenario 1					
MF (ACI)	5,336	17.0284	-	-	-
ACI (ACI)	8,100	18.0228	2,763	0.9944	2,779
Scenario 2					
MF (MF)	5,015	17.0033	-	-	-
ACI (MF)	7,892	17.9570	2,877	0.9537	3,016
Probabilistic – 75% reduction					
Scenario 1					
MF (ACI)	5,346	16.9755	-	-	-
ACI (ACI)	8,083	18.0442	2,737	1.0687	2,561
Scenario 2					
MF (MF)	5,023	16.9546	-	-	-
ACI (MF)	7,878	17.9253	2,854	0.9707	2,940

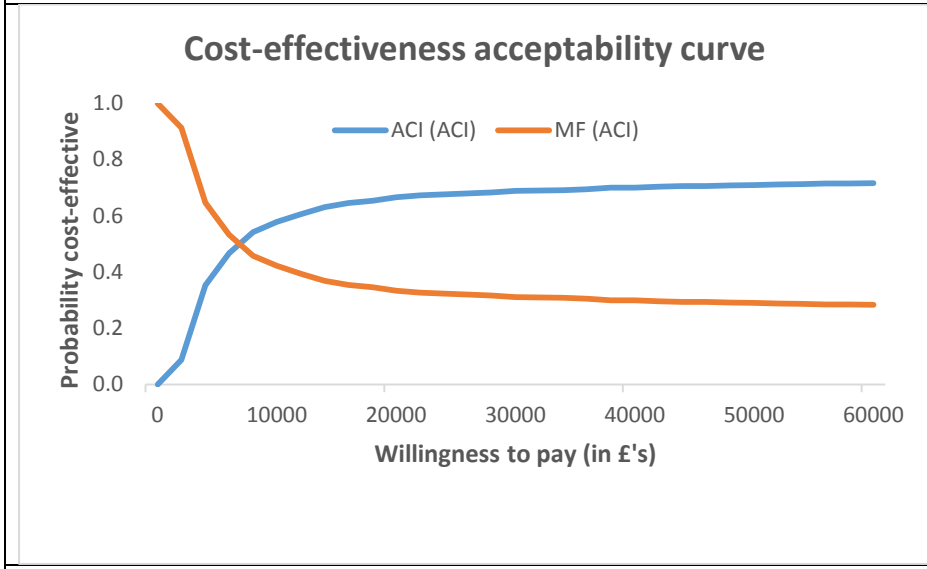
Figure 9a to Figure 9f present the cost-effectiveness acceptability curves for the sensitivity analysis for cell cost reductions for scenarios 1 and 2. For a 25% cell cost reduction – for scenario 1, if the decision maker was willing to pay £20,000, the probability that ACI was more cost-effective than MF was 65% (see Figure 9a) and for scenario 2, the probability that ACI was more cost-effective than MF was 58% (see Figure 9b). For a 50% cell cost reduction – for scenario 1, if the decision maker was willing to pay £20,000, the probability that ACI was more cost-effective than MF was 67% (see Figure 9c) and for scenario 2, the probability that ACI was more cost-effective than MF was 64% (see Figure 9d). For a 75% cell cost reduction – for scenario 1, if the decision maker was willing to pay £20,000, there was a 71% probability that ACI was more cost-effective than MF (see Figure 9e) and for scenario 2, there was a 70% probability that ACI was more cost-effective than MF (see Figure 9f). The graphs indicate that reductions in cell costs improves the cost-effectiveness of ACI compare to MF.



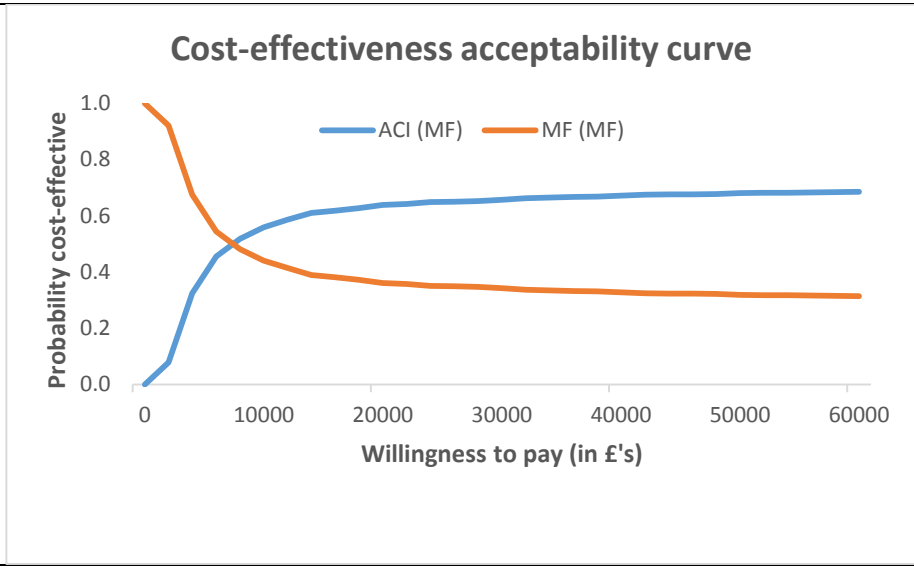
a: CEAC – 25% cell cost reduction: scenario 1



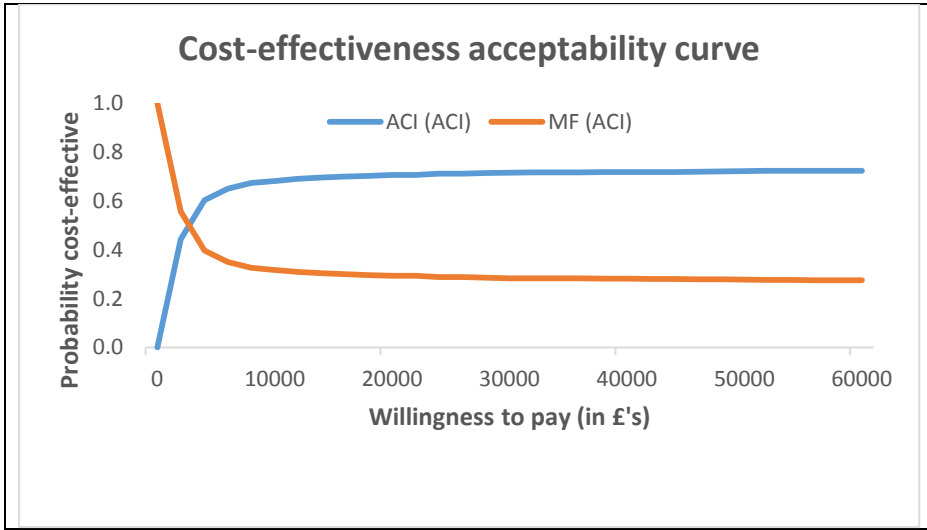
b: CEAC – 25% cell cost reduction: scenario 2



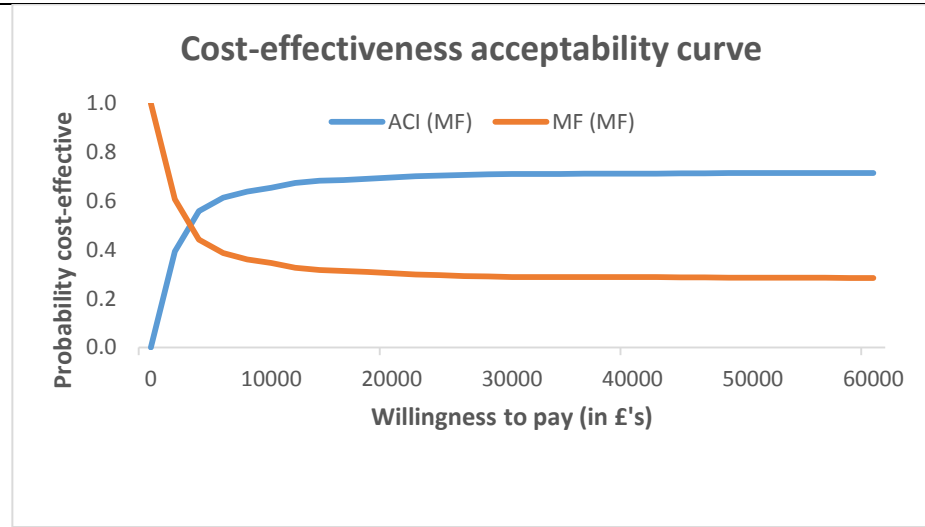
c: CEAC – 50% cell cost reduction: scenario 1



d: CEAC – 50% cell cost reduction: scenario 2



e: CEAC – 75% cell cost reduction: scenario 1



f: CEAC – 75% cell cost reduction: scenario 2

Figure 9. CEAC – cost reductions

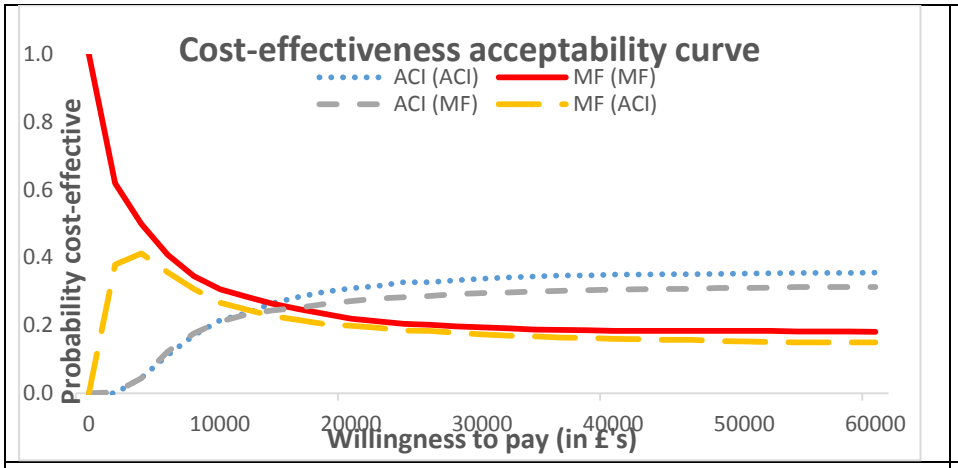
Table 19. Sensitivity cost-effectiveness results - cell cost reduction

Procedure	Total mean costs £	Total mean QALYs	Comparison	Incremental costs £	Incremental QALYs	ICER £ (cost per QALY gained)
Deterministic – 25% reduction						
MF (MF)	5,015	17.0033	-	-	-	-
MF (ACI)	6,183	17.0284	MF (ACI) v MF (MF)	1,168	0.0251*	46,564
ACI (MF)	15,892	17.9570	ACI (MF) v MF (ACI)	9,709	0.9287	10,455
ACI (ACI)	16,647	18.0228	ACI (ACI) v ACI (MF)	755	0.0658*	11,483
Probabilistic - 25% reduction						
MF (MF)	5,009	17.0086	-	-	-	-
MF (ACI)	6,183	17.0305	MF (ACI) v MF (MF)	1,174	0.0219*	53,619
ACI (MF)	15,880	17.9502	ACI (MF) v MF (ACI)	9,697	0.9197	10,453
ACI (ACI)	16,637	18.0497	ACI (ACI) v ACI (MF)	758	0.0994*	7,618
Deterministic – 50% reduction						
MF (MF)	5,015	17.0033	-	-	-	-
MF (ACI)	5,760	17.0284	MF (ACI) v MF (MF)	744	0.0251*	29,678
ACI (MF)	11,892	17.9570	ACI (MF) v MF (ACI)	6,132	0.9287	6,603
ACI (ACI)	12,373	18.0228	ACI (ACI) v ACI (MF)	481	0.0658*	7,319
Probabilistic - 50% reduction						
MF (MF)	5,020	16.9907	-	-	-	-
MF (ACI)	5,770	17.0250	MF (ACI) v MF (MF)	750	0.0343*	21,869
ACI (MF)	11,876	17.9123	ACI (MF) v MF (ACI)	6,106	0.8873	6,881
ACI (ACI)	12,362	18.0100	ACI (ACI) v ACI (MF)	486	0.0977*	4,979
Deterministic – 75% reduction						
MF (MF)	5,015	17.0033	-	-	-	-
MF (ACI)	5,336	17.0284	MF (ACI) v MF (MF)	321	0.0251*	12,792
ACI (MF)	7,892	17.9570	ACI (MF) v MF (ACI)	2,556	0.9287	2,752
ACI (ACI)	8,100	18.0228	ACI (ACI) v ACI (MF)	207	0.0658*	3,155
Probabilistic - 75% reduction						
MF (MF)	5,023	16.9546	-	-	-	-
MF (ACI)	5,346	16.9755	MF (ACI) v MF (MF)	322	0.0209*	15,430
ACI (MF)	7,878	17.9253	ACI (MF) v MF (ACI)	2,532	0.9498	2,666
ACI (ACI)	8,083	18.0442	ACI (ACI) v ACI (MF)	205	0.1189*	1,725

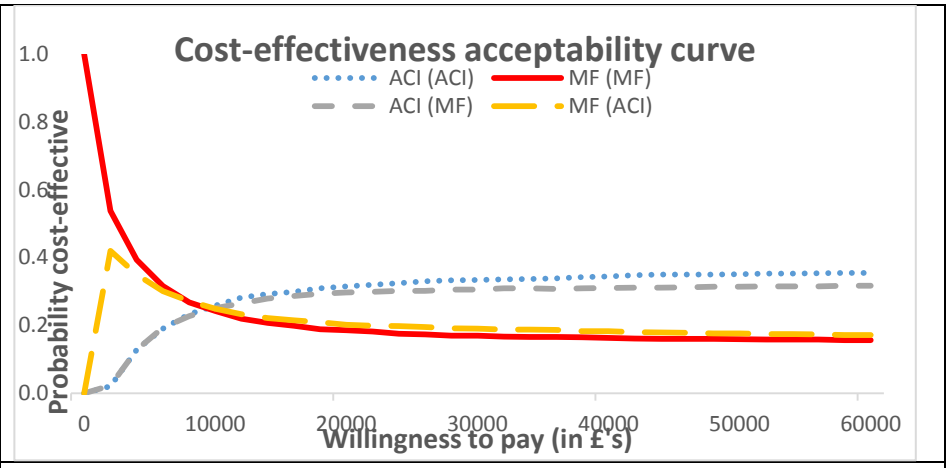
* As the incremental QALYs are near zero, the ICER can fluctuate widely

Table 19 shows the deterministic and probabilistic cost-effectiveness results for the lifetime horizon for cell cost reduction and results were ranked by least costly option. When the cost of cells was reduced by 25%, 50% and 75% these results were in line with the base-case cost-effectiveness results. That is, for the discounted deterministic results MF (MF) was the least costly option and had the fewest QALYs, whereas ACI (ACI) was the most expensive option but generated more QALYs. The deterministic incremental cost-effectiveness ratio between the two MF options: MF (ACI) vs MF (MF) was nearly £47,000; the ICER between ACI (MF) and MF (ACI) was just over £10,000; and the ICER between the two ACI options: ACI (ACI) vs ACI (MF) was just under £12,000 when there was a 25% reduction in costs. These ICER figures are £30,000, £6,500, and £7,300 respectively when there was a 50% reduction in costs and the corresponding figures are £13,000, £2,700, and £3,500 respectively when there was a 75% reduction in costs. For all cell cost reduction scenarios, both the deterministic and probabilistic results indicate that ACI as a first procedure was more cost-effective than MF as a first procedure and from these results, again we see that the cost of cells is a key driver of the cost-effectiveness estimates.

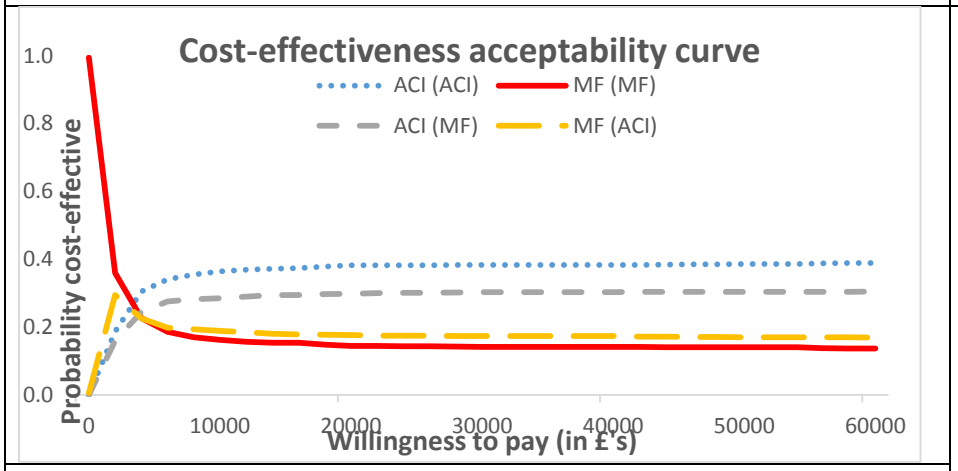
Figure 10 (a to c) presents the cost-effectiveness acceptability curves for the sensitivity analysis results for the cell cost reduction. The graphs clearly show that if the decision maker is willing to pay £20,000 then the probability that ACI (ACI) is more cost-effective than the other 3 comparisons is 32% for a 50% reduction in the costs of cells (although there is not much difference if MF was the second repair after the ACI) and 38% for a 75% reduction in the costs of cells. Whereas, if the decision maker pays £30,000 for a 25% reduction in the cost of cells then the probability that ACI (ACI) is more cost-effective than the other 3 comparisons is 34%. This suggests that ACI as first procedure is more cost-effective than MF as first procedure.



a: CEAC – 25% cell cost reduction



b: CEAC – 50% cell cost reduction



c: CEAC – 75% cell cost reduction

Figure 10. Cost-effectiveness acceptability curves – cell cost reduction

b) SA 2. Changing the time horizon

In the base-case analysis, a lifetime horizon was chosen with the starting age 33 years for the cohort. In this sensitivity analysis we have varied the time horizon (10, 20, 30, 40 and 50 years) to see how this affects the incremental cost-effectiveness ratio. Table 20 shows the sensitivity cost-effectiveness results for the different time horizons. For all time horizons, even though ACI was more costly than MF, there were more QALYs gained with ACI than MF. For the 10 year time horizon, the deterministic cost per QALY gain ratio for ACI compared with MF was £25,992 for scenario 1 and £27,388 for scenario 2. The cost per QALY gained for the two scenarios ranged from: £17k to £18k for a 20 year time horizon; £15k to £16k for the 30 year and 40 year time horizons; and £14k to £16k for the 50 year time horizon. For both scenarios, ACI as a first repair was more-cost-effective than MF as a first repair, the longer the time horizon. These results were of similar magnitudes and directions for the probabilistic results.

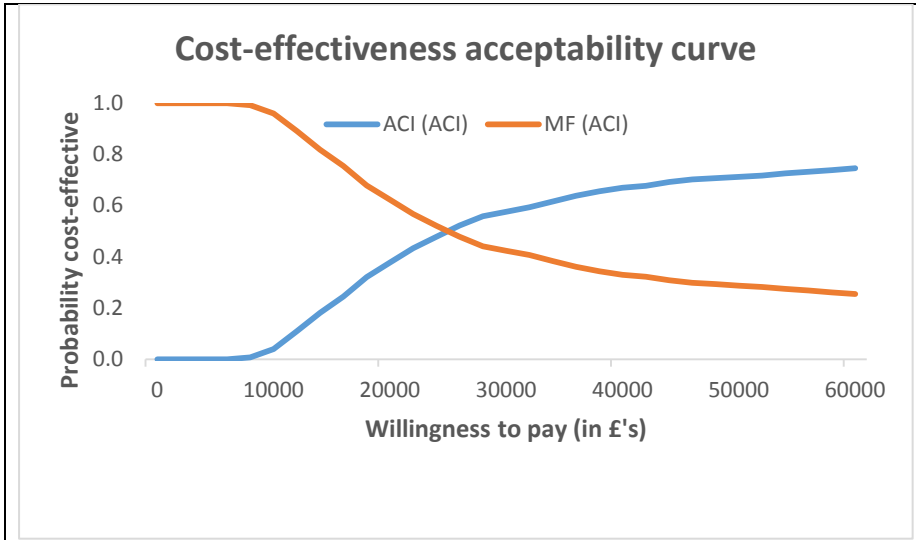
Table 20. Sensitivity cost-effectiveness results (by scenario) – changing the time horizon

Procedure	Total mean costs £	Total mean QALYs	Incremental costs £	Incremental QALYs	ICER £ (cost per QALY gained)
Deterministic – 10 year time horizon					
Scenario 1					
MF (ACI)	5,983	7.3030	-	-	-
ACI (ACI)	20,082	7.8454	14,098	0.5424	25,992
Scenario 2					
MF (MF)	4,498	7.2906	-	-	-
ACI (MF)	19,329	7.8321	14,831	0.5415	27,388
Probabilistic – 10 year time horizon					
Scenario 1					
MF (ACI)	5,989	7.2950	-	-	-
ACI (ACI)	20,075	7.8501	14,086	0.5550	25,379
Scenario 2					
MF (MF)	4,505	7.2845	-	-	-
ACI (MF)	19,326	7.8270	14,821	0.5425	27,320
Deterministic – 20 year time horizon					
Scenario 1					
MF (ACI)	6,104	11.2812	-	-	-
ACI (ACI)	20,340	12.1040	14,286	0.8228	17,301
Scenario 2					
MF (MF)	4,524	11.2587	-	-	-
ACI (MF)	19,384	12.0654	14,860	0.8067	18,421
Probabilistic – 20 year time horizon					
Scenario 1					
MF (ACI)	6,098	11.2630	-	-	-
ACI (ACI)	20,359	12.1136	14,261	0.8506	16,766
Scenario 2					
MF (MF)	4,526	11.2362	-	-	-
ACI (MF)	19,414	12.0625	14,888	0.8263	18,019
Deterministic – 30 year time horizon					
Scenario 1					

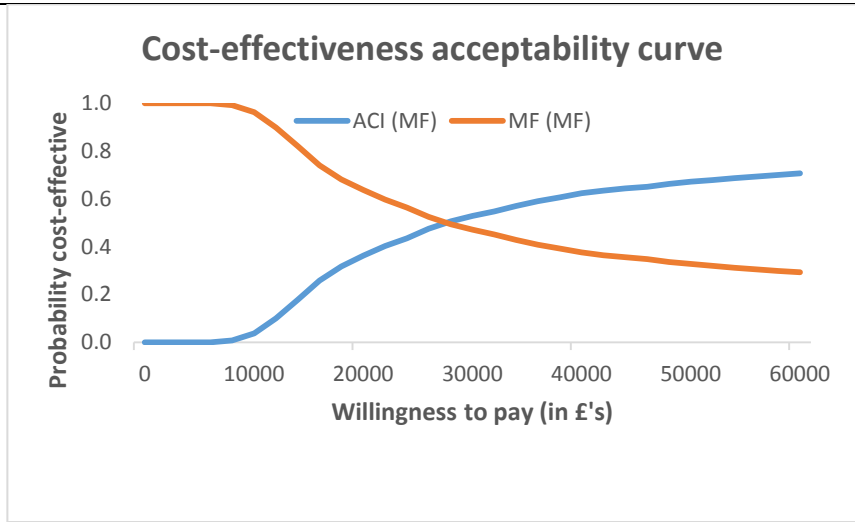
MF (ACI)	6,329	13.9997	-	-	-
ACI (ACI)	20,614	14.9318	14,285	0.9321	15,326
Scenario 2					
MF (MF)	4,739	13.9750	-	-	-
ACI (MF)	19,609	14.8774	14,871	0.9024	16,480
Probabilistic – 30 year time horizon					
Scenario 1					
MF (ACI)	6,326	14.0117	-	-	-
ACI (ACI)	20,642	14.9494	14,316	0.9377	15,267
Scenario 2					
MF (MF)	4,728	13.9748	-	-	-
ACI (MF)	19,628	14.8754	14,900	0.9006	16,545
Deterministic – 40 year time horizon					
Scenario 1					
MF (ACI)	6,492	15.7604	-	-	-
ACI (ACI)	20,798	16.7368	14,306	0.9764	14,652
Scenario 2					
MF (MF)	4,901	15.7354	-	-	-
ACI (MF)	19,775	16.6747	14,875	0.9393	15,836
Probabilistic – 40 year time horizon					
Scenario 1					
MF (ACI)	6,494	15.7558	-	-	-
ACI (ACI)	20,763	16.7219	14,269	0.9662	14,768
Scenario 2					
MF (MF)	4,900	15.7279	-	-	-
ACI (MF)	19,376	16.6504	14,837	0.9225	16,083
Deterministic – 50 year time horizon					
Scenario 1					
MF (ACI)	6,579	16.7164	-	-	-
ACI (ACI)	20,891	17.7078	14,313	0.9914	14,437
Scenario 2					
MF (MF)	4,987	16.6913	-	-	-
ACI (MF)	19,864	17.6427	14,876	0.9514	15,636
Probabilistic – 50 year time horizon					
Scenario 1					
MF (ACI)	6,557	16.7119	-	-	-
ACI (ACI)	20,841	17.6964	14,284	0.9845	14,509
Scenario 2					
MF (MF)	4,974	16.6777	-	-	-
ACI (MF)	19,820	17.6182	14,845	0.9405	15,785

Figure 11 (a to j) presents the cost-effectiveness acceptability curves for the sensitivity analysis for the different time horizons for scenarios 1 and 2. For the 10 year time horizon – for scenario 1, if the decision maker was willing to pay £20,000, the probability that MF was more cost-effective than ACI was 62% (see Figure 11a) and for scenario 2, MF was 645 more likely to be cost-effective than ACI (see Figure 11b). ACI became more cost-effective than MF when the decision maker was willing to pay approximately £26,000 for scenario 1 and £28,000 for scenario 2. For all other time horizons, the probability that ACI was more cost-effective than MF was approximately 55% for both scenarios

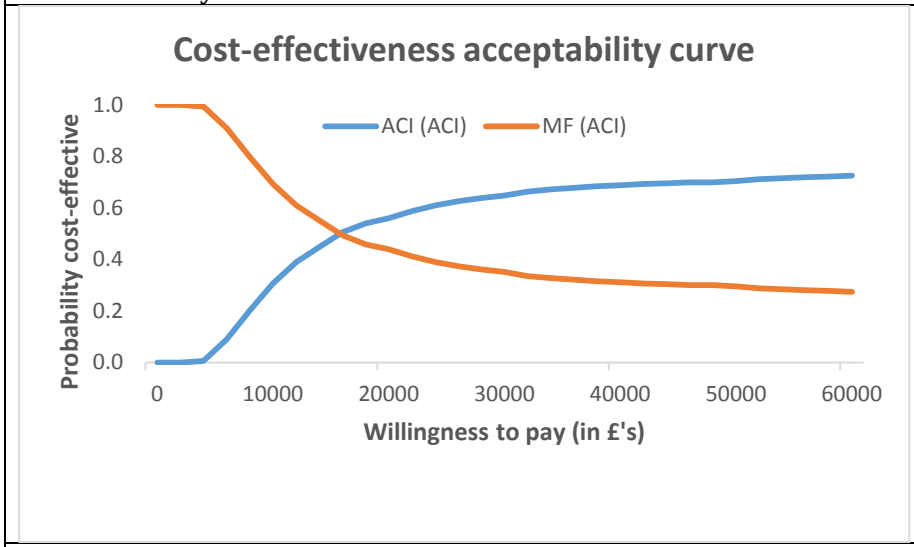
when the decision maker was willing to pay £20,000. The results highlighted that for the longer time horizons, ACI as a first repair was more cost-effective than MF as a first repair.



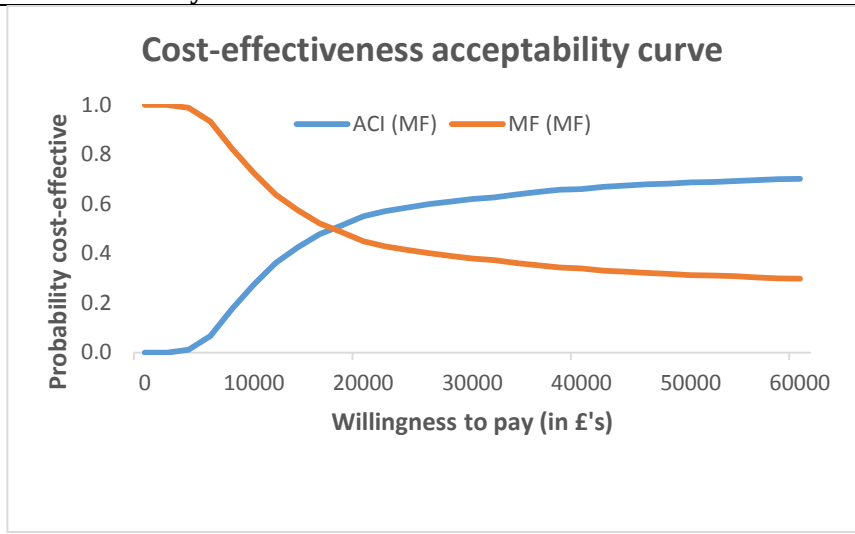
a: CEAC – 10 year time horizon: scenario 1



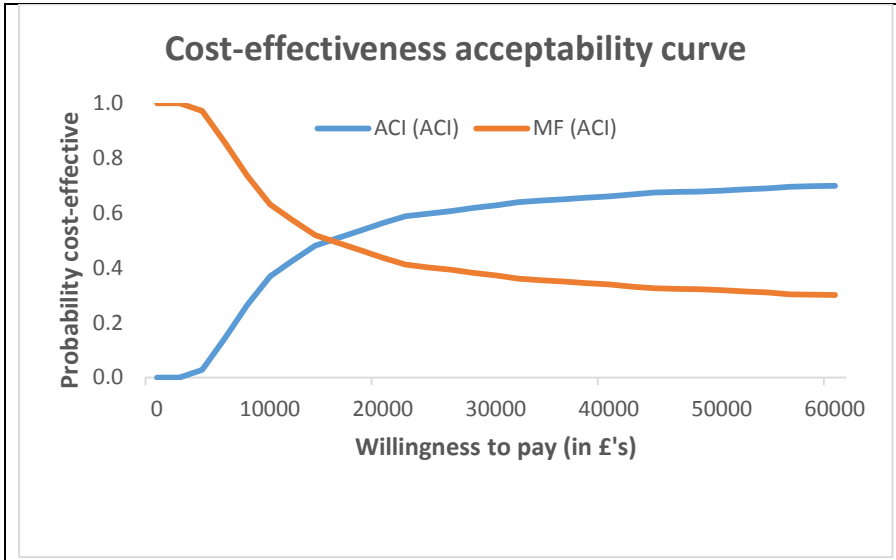
b: CEAC – 10 year time horizon: scenario 2



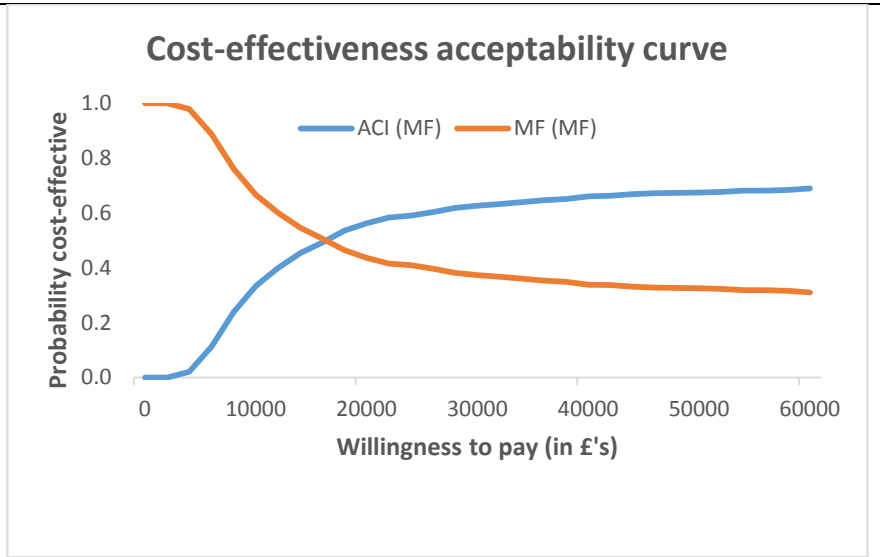
c: CEAC – 20 year time horizon: scenario 1



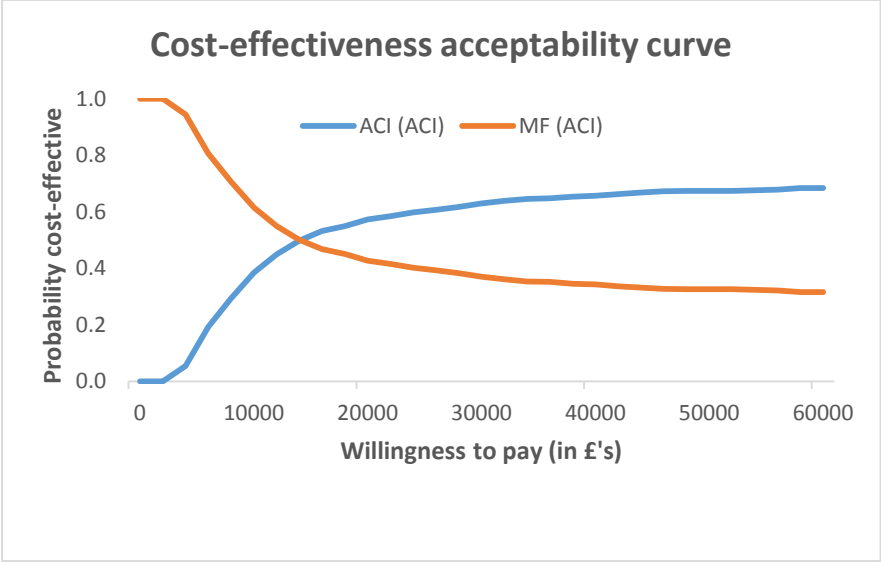
d: CEAC – 20 year time horizon: scenario 2



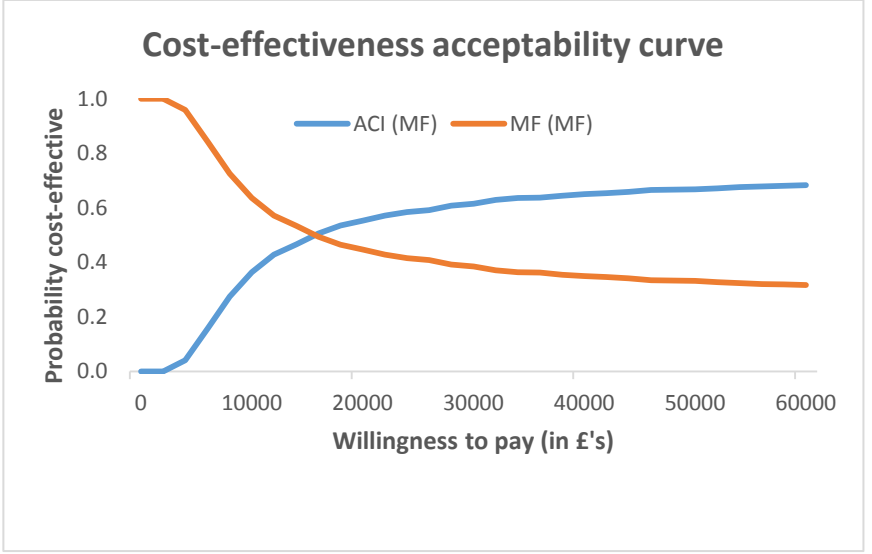
e: CEAC – 30 year time horizon: scenario 1



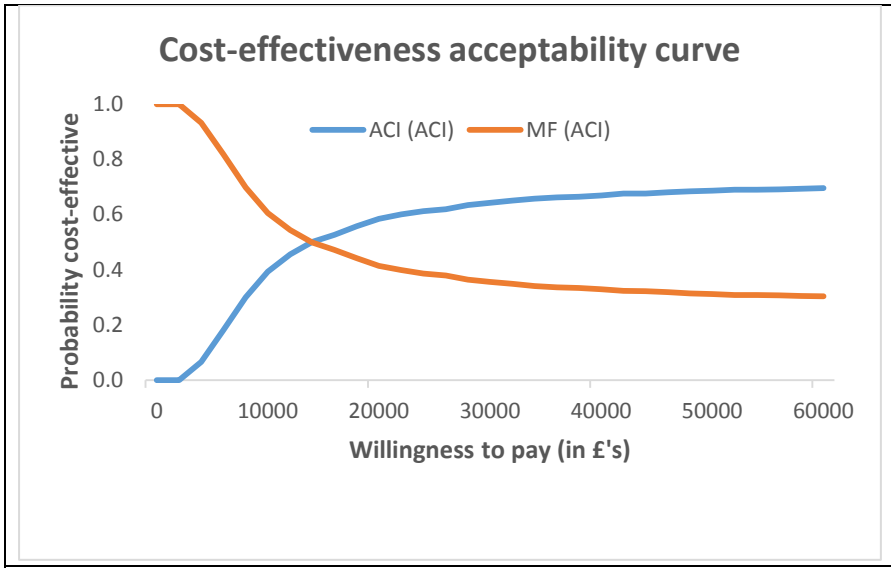
f: CEAC – 30 year time horizon: scenario 2



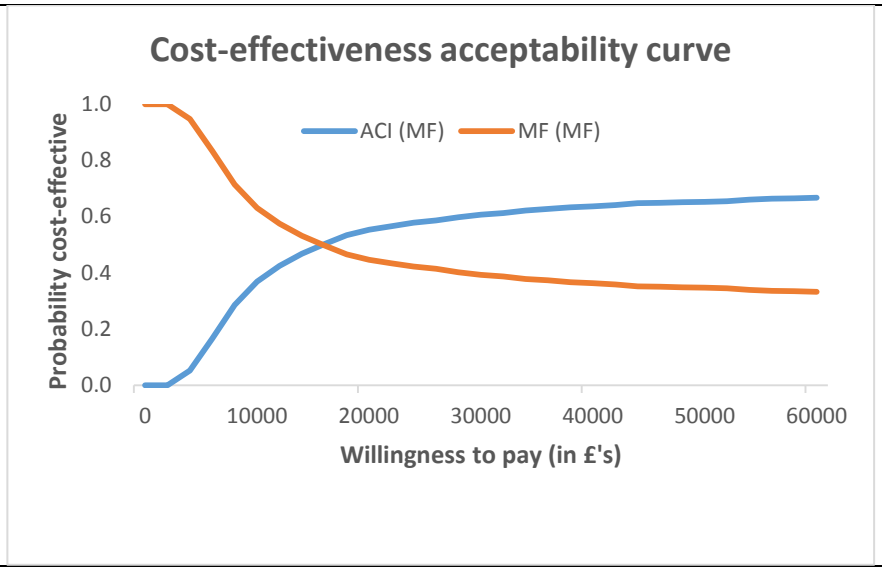
g: CEAC – 40 year time horizon: scenario 1



h: CEAC – 40 year time horizon: scenario 2



i: CEAC – 50 year time horizon: scenario 1



j: CEAC – 50 year time horizon: scenario 2

Figure 11. CEAC – different time horizons

Table 21 shows the deterministic and probabilistic cost-effectiveness results for the different time horizons and results were ranked by the least costly option. When comparing the two initial MF options: MF (MF) vs. MF (ACI) the deterministic ICER for a 10 year time horizon was over £120,000 For the same time period the deterministic ICER for the two initial ACI options: ACI (ACI) vs ACI (MF) was approximately half of this at £57,000. For the two initial ACI options, the deterministic ICER falls to just under £25,000 for a 20 year time horizon; and for the 30 year time horizon the ICER is just under £19,000. For both the 40 and 50 year time horizons (for the two initial ACI options), the deterministic ICER is very similar to the base-case ICER. The clear reason why the shorter time horizons are not cost-effective is due to the costs of ACI occurring at the start of the model and the benefits appearing much later, especially in terms of the reduced need for total knee replacements and fewer people going to the no further repair or no further knee replacement health states (where the utility is lower).

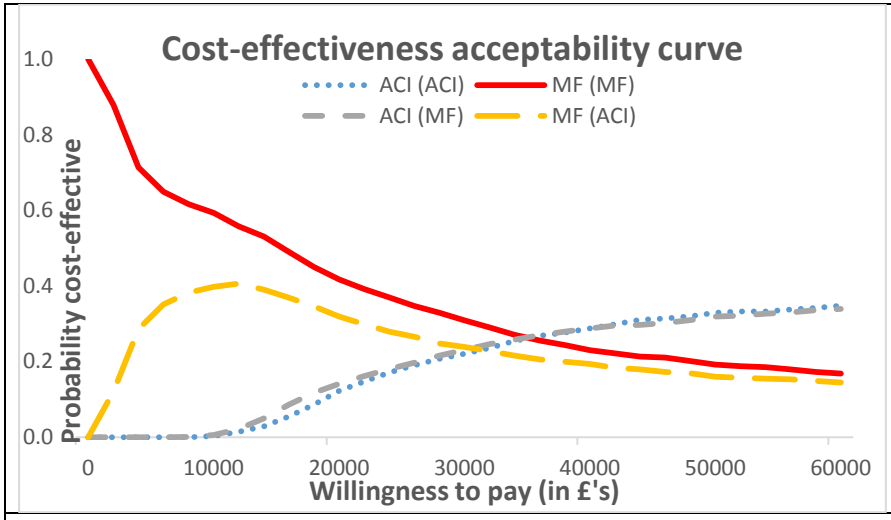
Table 21. Sensitivity cost-effectiveness results – changing the time horizon

Procedure	Total mean costs £	Total mean QALYs	Comparison	Incremental costs £	Incremental QALYs	ICER £ (cost per QALY gained)
Deterministic – 10 year time horizon						
MF (MF)	4,498	7.2906	-	-	-	-
MF (ACI)	5,983	7.3030	MF (ACI) v MF (MF)	1,485	0.0124*	120,252
ACI (MF)	19,329	7.8321	ACI (MF) v MF (ACI)	13,346	0.5292	25,220
ACI (ACI)	20,082	7.8454	ACI (ACI) v ACI (MF)	753	0.0132*	56,816
Probabilistic - 10 year time horizon						
MF (MF)	4,505	7.2845	-	-	-	-
MF (ACI)	5,989	7.2950	MF (ACI) v MF (MF)	1,484	0.0105*	140,705
ACI (MF)	19,326	7.8270	ACI (MF) v MF (ACI)	13,337	0.5319	25,072
ACI (ACI)	20,075	7.8501	ACI (ACI) v ACI (MF)	749	0.0231*	32,448
Deterministic – 20 year time horizon						
MF (MF)	4,524	11.2587	-	-	-	-
MF (ACI)	6,104	11.2812	MF (ACI) v MF (MF)	1,580	0.0225*	70,152
ACI (MF)	19,384	12.0654	ACI (MF) v MF (ACI)	13,280	0.7842	16,935
ACI (ACI)	20,340	12.1040	ACI (ACI) v ACI (MF)	955	0.0386*	24,742
Probabilistic - 20 year time horizon						
MF (MF)	4,526	11.2362	-	-	-	-
MF (ACI)	6,098	11.2630	MF (ACI) v MF (MF)	1,572	0.0268*	58,704
ACI (MF)	19,414	12.0625	ACI (MF) v MF (ACI)	13,317	0.7995	16,656

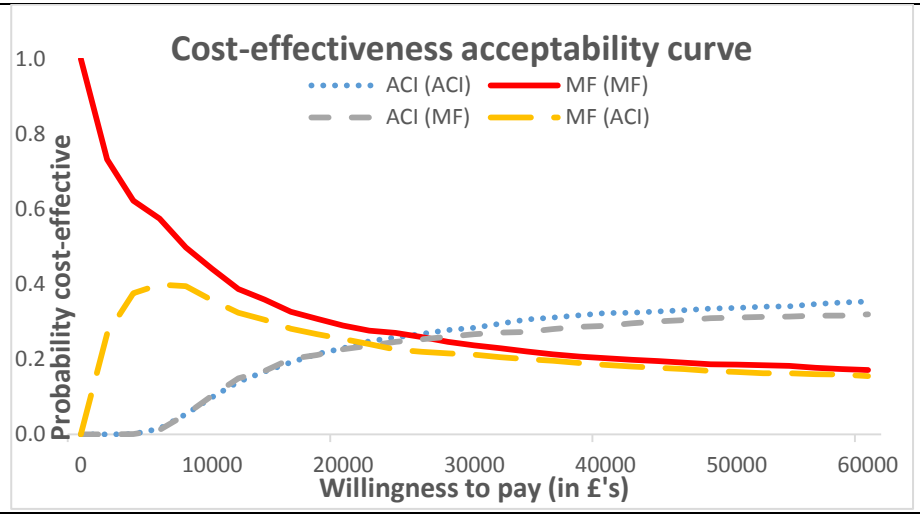
ACI (ACI)	20,359	12.1136	ACI (ACI) v ACI (MF)	944	0.0511*	18,486
Deterministic – 30 year time horizon						
MF (MF)	4,739	13.9750	-	-	-	-
MF (ACI)	6,329	13.9997	MF (ACI) v MF (MF)	1,590	0.0247*	64,495
ACI (MF)	19,609	14.8774	ACI (MF) v MF (ACI)	13,280	0.8777	15,131
ACI (ACI)	20,614	14.9318	ACI (ACI) v ACI (MF)	1,005	0.0544*	18,472
Probabilistic - 30 year time horizon						
MF (MF)	4,728	13.9748	-	-	-	-
MF (ACI)	6,326	14.0117	MF (ACI) v MF (MF)	1,598	0.0369*	43,334
ACI (MF)	19,628	14.8754	ACI (MF) v MF (ACI)	13,302	0.8637	15,401
ACI (ACI)	20,642	14.9494	ACI (ACI) v ACI (MF)	1,014	0.0740*	13,705
Deterministic – 40 year time horizon						
MF (MF)	4,901	15.7354	-	-	-	-
MF (ACI)	6,492	15.7604	MF (ACI) v MF (MF)	1,591	0.0250*	63,579
ACI (MF)	19,775	16.6747	ACI (MF) v MF (ACI)	13,284	0.9143	14,529
ACI (ACI)	20,798	16.7368	ACI (ACI) v ACI (MF)	1,022	0.0621*	16,466
Probabilistic - 40 year time horizon						
MF (MF)	4,900	15.7279	-	-	-	-
MF (ACI)	6,494	15.7558	MF (ACI) v MF (MF)	1,594	0.0276*	57,810
ACI (MF)	19,736	16.6504	ACI (MF) v MF (ACI)	13,243	0.8946	14,803
ACI (ACI)	20,763	16.7219	ACI (ACI) v ACI (MF)	1,026	0.0716*	14,336
Deterministic – 50 year time horizon						
MF (MF)	4,987	16.6913	-	-	-	-
MF (ACI)	6,579	16.7164	MF (ACI) v MF (MF)	1,592	0.0251*	63,458
ACI (MF)	19,864	17.6427	ACI (MF) v MF (ACI)	13,285	0.9263	14,341
ACI (ACI)	20,891	17.7078	ACI (ACI) v ACI (MF)	1,028	0.0651*	15,793
Probabilistic - 50 year time horizon						
MF (MF)	4,974	16.6777	-	-	-	-
MF (ACI)	6,557	16.7119	MF (ACI) v MF (MF)	1,583	0.0341*	46,395
ACI (MF)	19,820	17.6182	ACI (MF) v MF (ACI)	13,262	0.9063	14,633
ACI (ACI)	20,841	17.6964	ACI (ACI) v ACI (MF)	1,022	0.0782*	13,073

* As the incremental QALYs are near zero, the ICER can fluctuate widely

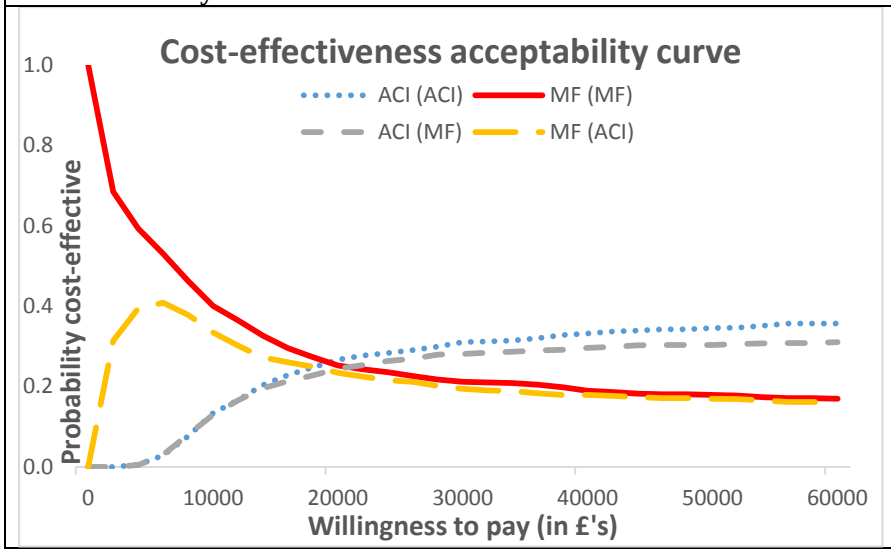
Figure 12 (a to e) presents the cost-effectiveness acceptability curves for the sensitivity analysis results for the different time horizons. The graphs suggest that for the 10 year time horizon, MF (MF) is the most cost-effective option if the decision maker is willing to pay £30,000 per QALY; over £36,000 the most cost-effective option is ACI as a first repair and if a second repair is this could either be ACI or MF. For the 20 year time horizon, MF (MF) appears the most cost-effective option if the decision maker is willing to pay £22,000 per QALY; over £26,000 per QALY the most cost-effective option is ACI (ACI); ACI as a first repair and if a second repair is needed this should also be ACI. As the time horizon increases ACI (ACI) - ACI as a first repair and if a second repair is needed this should also be an ACI, is probably more cost-effective than the other 3 sequences: so for example, if the decision maker is willing to pay £24,000, then the probability that ACI (ACI) is more cost-effective for both the 30 and 40 year time horizons is 28% and the probability that ACI (ACI) is more cost-effective for the 50 year time horizon is 29%.

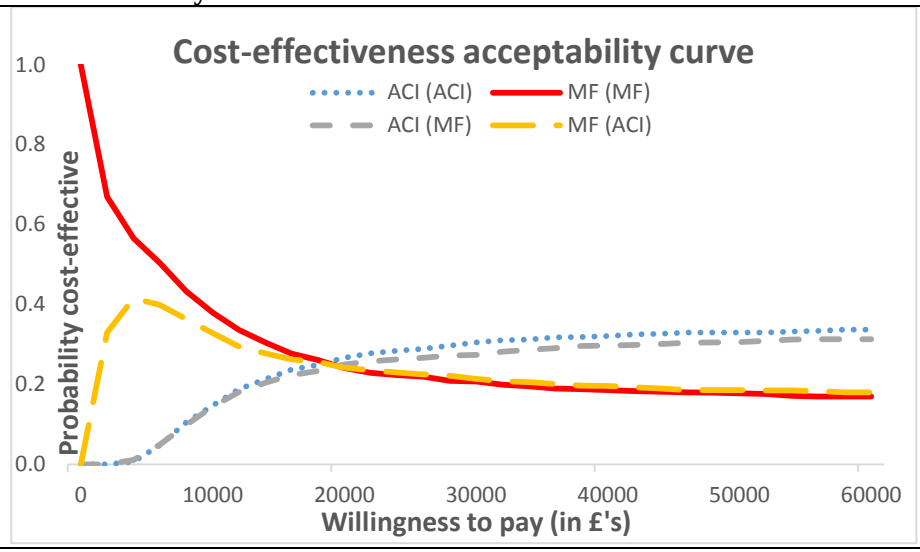


a: CEAC – 10 year time horizon



b: CEAC – 20 year time horizon





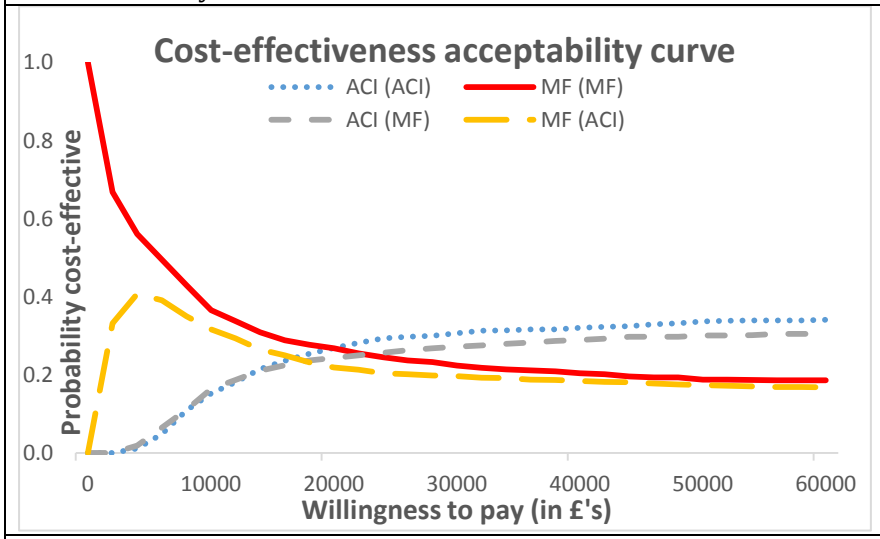
c: CEAC – 30 year time horizon	d: CEAC – 40 year time horizon
	
e: CEAC – 50 year time horizon	

Figure 12. Cost-effectiveness acceptability curves – changing the time horizon

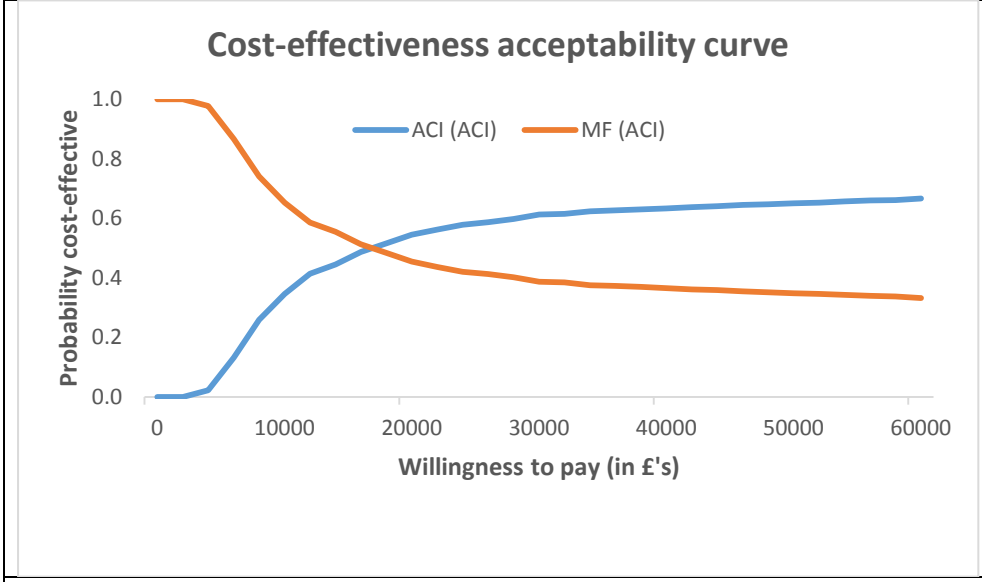
c) SA 3. MF done as a day case procedure

In the base-case analysis, according to clinical advice we have used a cost for MF as an inpatient procedure (£3,020); however, we know that sometimes this procedure is done as day case. In the sensitivity analysis we have assumed that MF is done as a day case procedure at a cost of £1,034. Table 22 shows the sensitivity cost-effectiveness results for MF as a day case procedure. The costs for MF have fallen but the QALY gain does not change. Hence, ACI as a first repair is still the most cost-effective procedure compared with MF as a first repair with an ICER of just over £16,000 (scenario 1) and just under £18,000 (scenario 2).

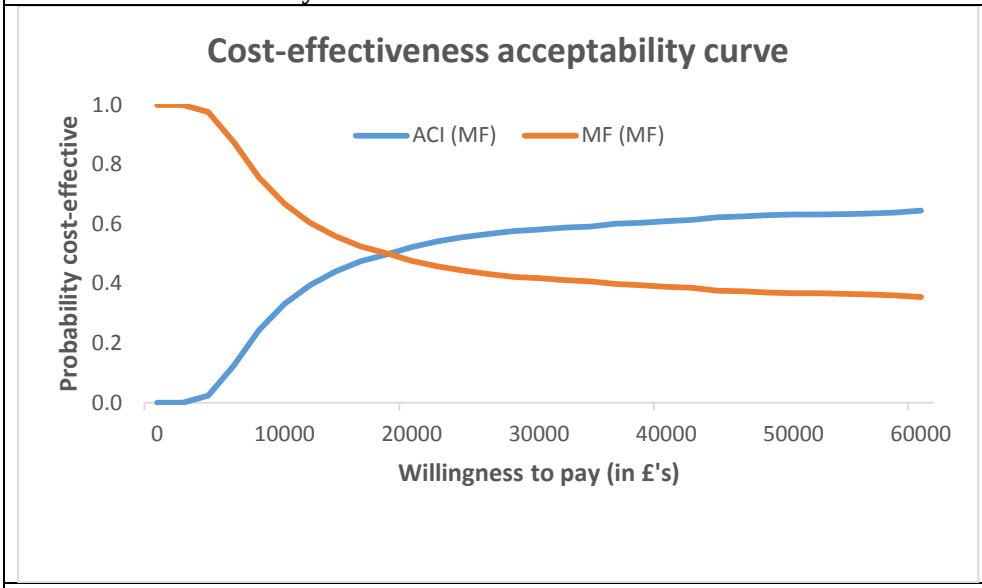
Table 22. Sensitivity cost-effectiveness results (by scenario) – MF procedure as a day case surgery and not as an inpatient

Procedure	Total mean costs £	Total mean QALYs	Incremental costs £	Incremental QALYs	ICER £ (cost per QALY gained)
Deterministic					
Scenario 1					
MF (ACI)	4,621	17.0284	-	-	-
ACI (ACI)	20,921	18.0228	16,300	0.9944	16,391
Scenario 2					
MF (MF)	2,819	17.0033	-	-	-
ACI (MF)	19,756	17.9570	16,937	0.9537	17,758
Probabilistic					
Scenario 1					
MF (ACI)	4,620	17.0412	-	-	-
ACI (ACI)	20,951	17.9975	16,332	0.9563	17,078
Scenario 2					
MF (MF)	2,811	17.0137	-	-	-
ACI (MF)	19,788	17.9065	16,977	0.8928	19,017

Figure 13 (a and b) presents the cost-effectiveness acceptability curves for MF as a day case procedure for scenarios 1 and 2, respectively. For scenario 1, if the decision maker was willing to pay £20,000, the probability that ACI was more cost-effective than MF was 55% (see Figure 13a) and the probability that ACI was more cost-effective than MF was 52% (see Figure 13b).



a: CEAC – MF as a day case: scenario 1



b: CEAC – MF as a day case: scenario 2

Figure 13. CEAC - MF as a day case

Table 23 presents the deterministic and probabilistic cost-effectiveness results. Compared with the base-case analysis, even though the costs for MF have fallen, there is no change in the QALYs. The ICERs between the different options were in line with the base-case results and initial ACI appears more cost-effective than initial MF and for those that need a second repair after the first ACI, this should be another ACI.

Table 23. Sensitivity cost-effectiveness results – MF procedure as a day case surgery and not as an inpatient

Procedure	Total mean costs £	Total mean QALYs	Comparison	Incremental costs £	Incremental QALYs	ICER £ (cost per QALY gained)
Deterministic						
MF (MF)	2,819	17.0033	-	-	-	-
MF (ACI)	4,621	17.0284	MF (ACI) v MF	1,802	0.0251*	71,832

			(MF)			
ACI (MF)	19,756	17.9570	ACI (MF) v MF (ACI)	15,135	0.9287	16,298
ACI (ACI)	20,921	18.0228	ACI (ACI) v ACI (MF)	1,165	0.0658*	17,715
Probabilistic						
MF (MF)	2,811	17.0137	-	-	-	-
MF (ACI)	4,620	17.0412	MF (ACI) v MF (MF)	1,809	0.0275*	65,784
ACI (MF)	19,788	17.9065	ACI (MF) v MF (ACI)	15,169	0.8653	17,531
ACI (ACI)	20,951	17.9975	ACI (ACI) v ACI (MF)	1,163	0.0910*	12,777

* As the incremental QALYs are near zero, the ICER can fluctuate widely

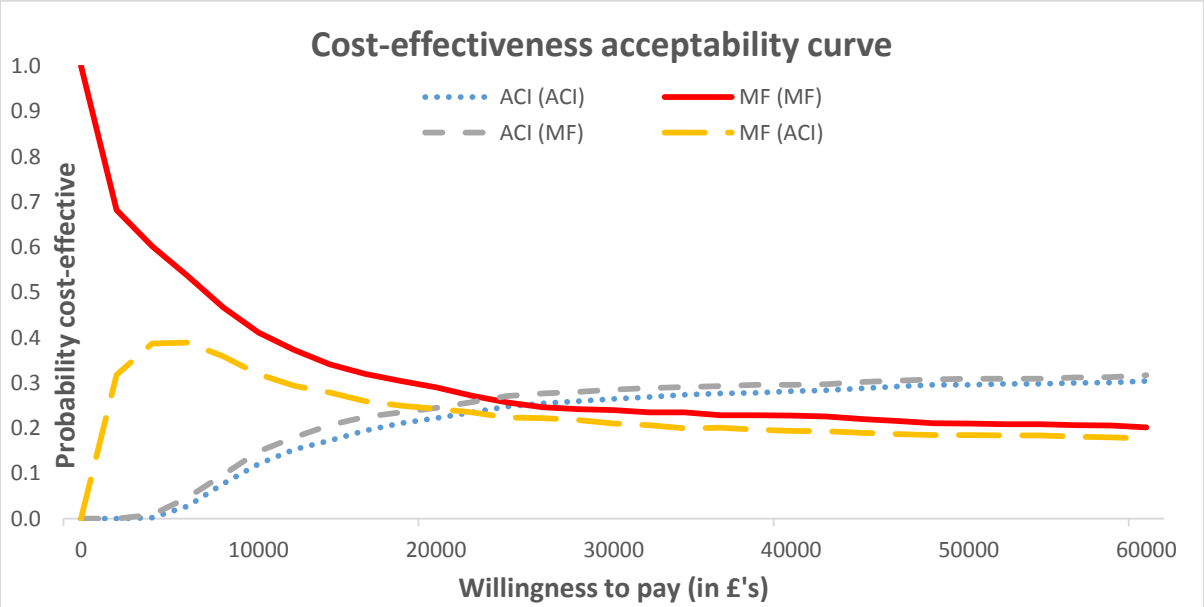


Figure 14. Cost-effectiveness acceptability curves – MF as a day case procedure

Figure 14 presents the cost-effectiveness acceptability curve and the graph highlights that if the decision maker is willing to pay less than £22,000 then MF (MF) is the most cost-effective option. If willing to pay more than £24,000, then ACI (MF) is the most cost-effective option – that is, the first repair should be ACI and if a second repair is needed this should be MF due to the lower costs (even though having an ACI as a second repair generates more QALYs).

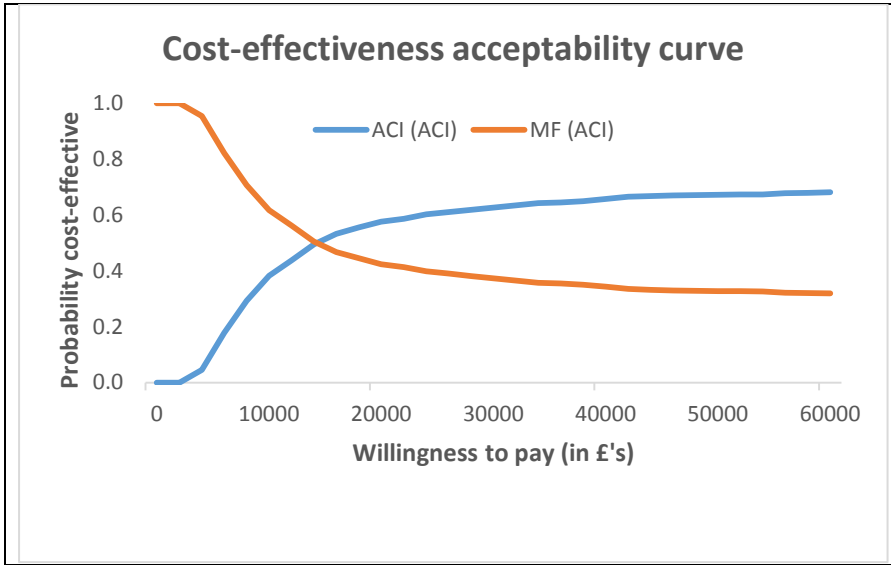
d) SA 4. Improving the success rates of MF

In this sensitivity analysis we have conducted a 'what if' scenario where we have assumed that the duration of success for MF increases: a) by 20% and b) by 40%. Table 24 shows the sensitivity cost-effectiveness results by scenario for the increase in the duration of success for MF. ACI was still more costly than MF, there were more QALYs gained with ACI than MF; even though there was a slight fall in the incremental QALYs gained compared with the base-case results, this was not enough to change the ICERs. For both scenarios, ACI as a first repair was more-cost-effective than MF as a first repair. These results were of similar magnitudes and directions for the probabilistic results.

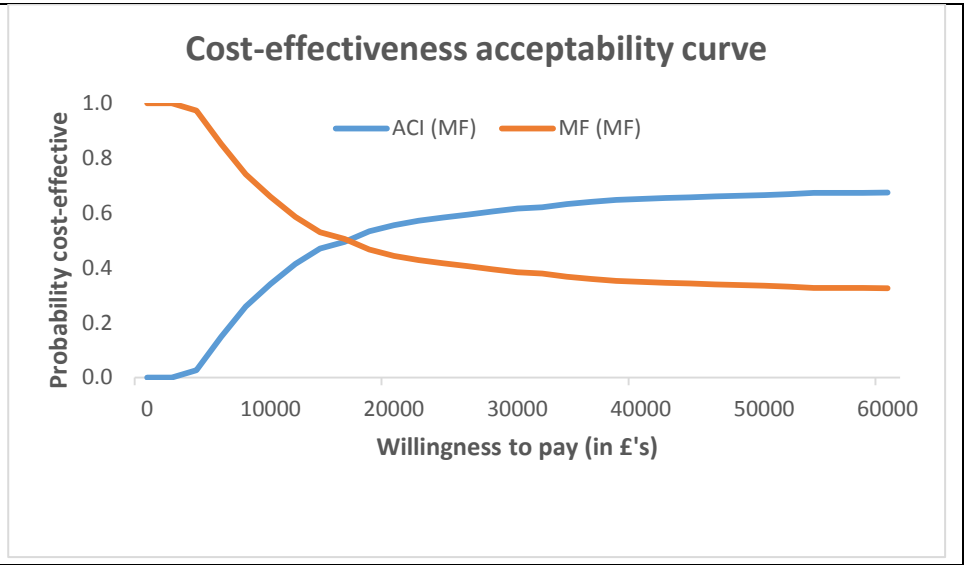
Table 24. Sensitivity cost-effectiveness results (by scenario) – improving the success rates of MF

Procedure	Total mean costs £	Total mean QALYs	Incremental costs £	Incremental QALYs	ICER £ (cost per QALY gained)
Deterministic – 20% increase in success rates					
Scenario 1					
MF (ACI)	6,392	17.0756	-	-	-
ACI (ACI)	20,921	18.0228	14,529	0.9472	15,338
Scenario 2					
MF (MF)	4,969	17.0607	-	-	-
ACI (MF)	19,892	17.9639	14,923	0.9033	16,521
Probabilistic - 20% increase in success rates					
Scenario 1					
MF (ACI)	6,387	17.0546	-	-	-
ACI (ACI)	20,895	18.0271	14,509	0.9725	14,919
Scenario 2					
MF (MF)	4,954	17.0403	-	-	-
ACI (MF)	19,856	17.9429	14,901	0.9027	16,508
Deterministic – 40% increase in success rates					
Scenario 1					
MF (ACI)	5,698	17.0787	-	-	-
ACI (ACI)	20,921	18.0228	15,223	0.9441	16,125
Scenario 2					
MF (MF)	4,820	17.0758	-	-	-
ACI (MF)	19,892	17.9741	15,072	0.8983	16,778
Probabilistic - 40% increase in success rates					
Scenario 1					
MF (ACI)	5,682	17.0535	-	-	-
ACI (ACI)	20,975	18.0331	15,292	0.9796	15,611
Scenario 2					
MF (MF)	4,803	17.0520	-	-	-
ACI (MF)	19,939	17.9887	15,136	0.9367	16,159

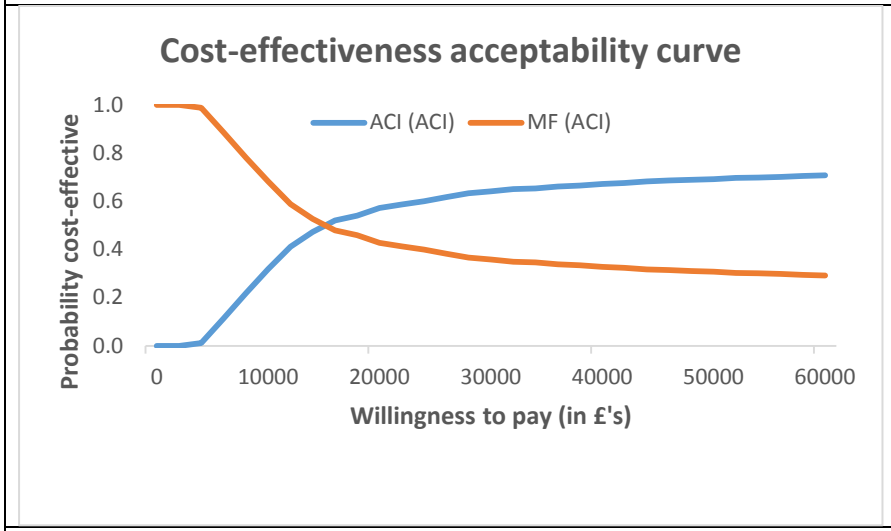
Figure 15a and Figure 15d presents the cost-effectiveness acceptability curves for the sensitivity analysis for the increase in the duration of success for MF for scenarios 1 and 2. For a 20% increase in the duration of success for MF – for scenario 1, if the decision maker was willing to pay £20,000, the probability that ACI was more cost-effective than MF was 58% (see Figure 15a) and for scenario 2, the probability that ACI was more cost-effective than MF was 56% (see Figure 15b). For a 40% increase in the duration of success for MF – these probability figures were 57% (see Figure 15c) and 55% (see Figure 15d), respectively.



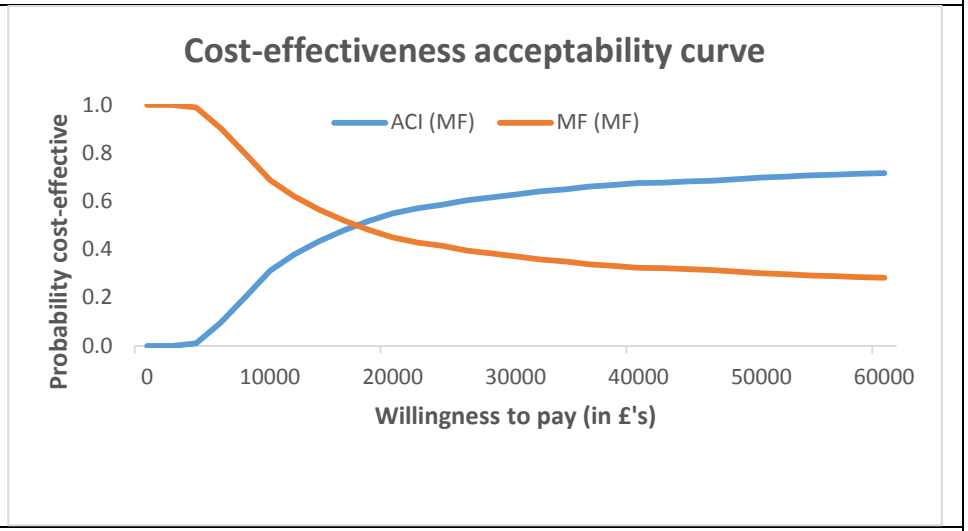
a: CEAC – 20% increase in MF success rate: scenario 1



b: CEAC – 20% increase in MF success rate: scenario 2



c: CEAC – 40% increase in MF success rate: scenario 1



d: CEAC – 40% increase in MF success rate: scenario 2

Figure 15. CEAC –increase in MF success rate

Table 25. Sensitivity cost-effectiveness results – improving the success rates of MF

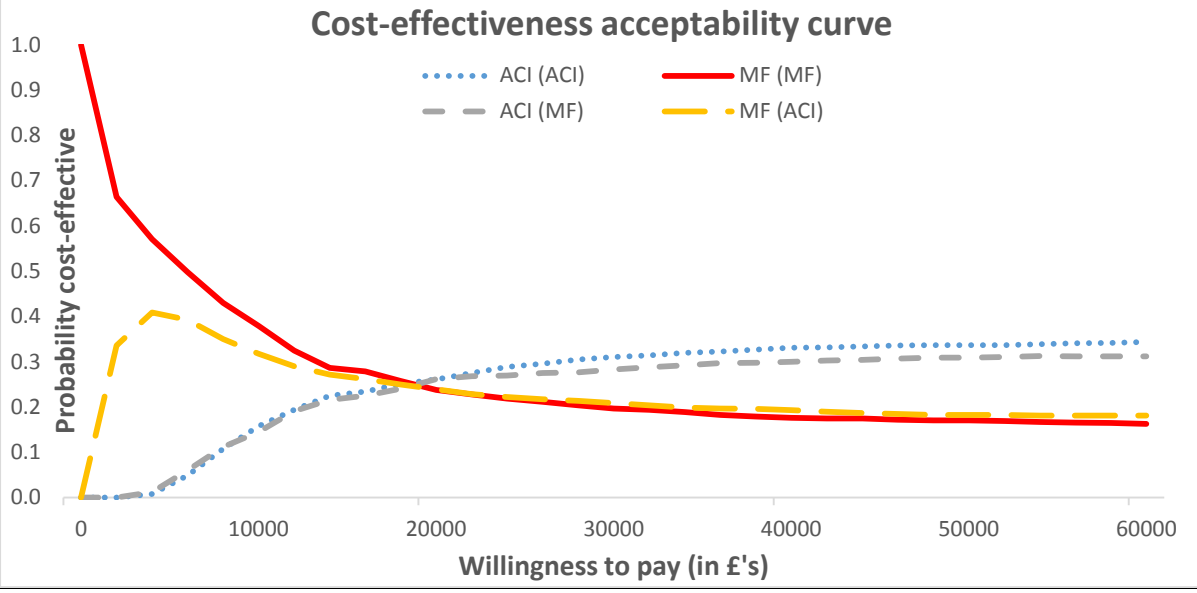
Procedure	Total mean costs £	Total mean QALYs	Comparison	Incremental costs £	Incremental QALYs	ICER £ (cost per QALY gained)
Deterministic – 20% increase in success rates						
MF (MF)	4,969	17.0607	-	-	-	-
MF (ACI)	6,392	17.0756	MF (ACI) v MF (MF)	1,423	0.0149*	95,618
ACI (MF)	19,892	17.9639	ACI (MF) v MF (ACI)	13,500	0.8884	15,196
ACI (ACI)	20,921	18.0228	ACI (ACI) v ACI (MF)	1,029	0.0589*	17,480
Probabilistic - 20% increase in success rates						
MF (MF)	4,954	17.0403	-	-	-	-
MF (ACI)	6,387	17.0546	MF (ACI) v MF (MF)	1,433	0.0144*	99,812
ACI (MF)	19,856	17.9429	ACI (MF) v MF (ACI)	13,469	0.8883	15,162
ACI (ACI)	20,895	18.0271	ACI (ACI) v ACI (MF)	1,040	0.0842*	12,356
Deterministic – 40% increase in success rates						
MF (MF)	4,820	17.0758	-	-	-	-
MF (ACI)	5,698	17.0787	MF (ACI) v MF (MF)	878	0.0029*	301,260
ACI (MF)	19,892	17.9741	ACI (MF) v MF (ACI)	14,194	0.8954	15,852
ACI (ACI)	20,921	18.0228	ACI (ACI) v ACI (MF)	1,029	0.0487*	21,130
Probabilistic - 40% increase in success rates						
MF (MF)	4,803	17.0520	-	-	-	-
MF (ACI)	5,682	17.0535	MF (ACI) v MF (MF)	880	0.0015*	592,407
ACI (MF)	19,939	17.9887	ACI (MF) v MF (ACI)	14,256	0.9352	15,244
ACI (ACI)	20,975	18.0331	ACI (ACI) v ACI (MF)	1,036	0.0443*	23,356

* As the incremental QALYs are near zero, the ICER can fluctuate widely

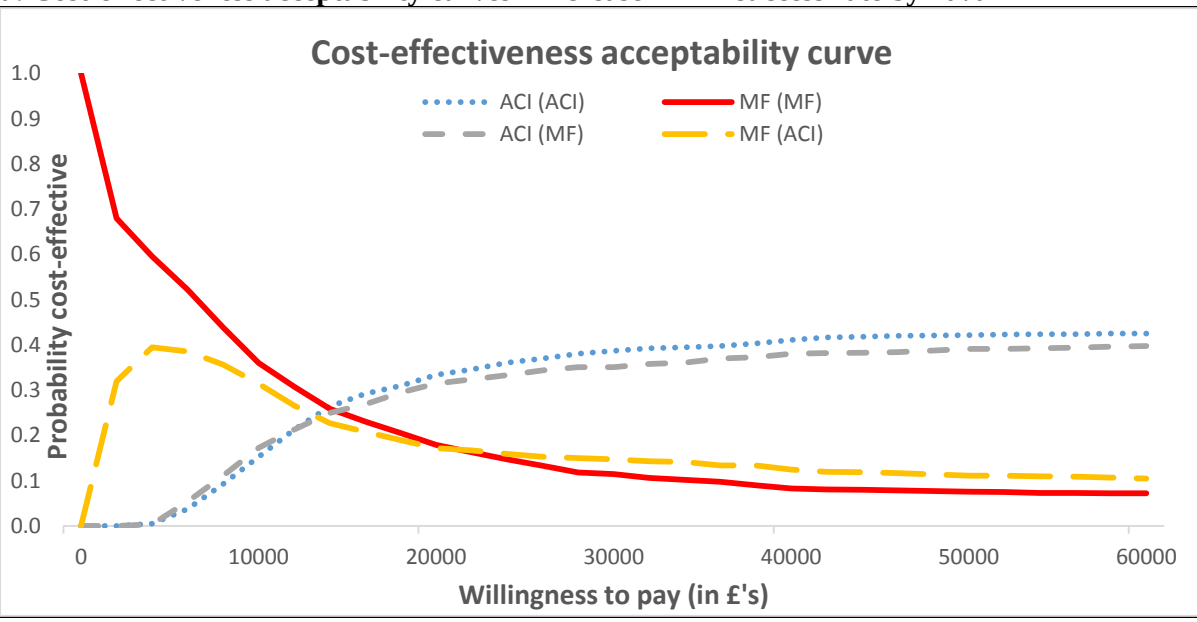
Table 25 presents the deterministic and probabilistic cost-effectiveness results. The costs of MF have fallen slightly and also the QALYs for MF have increased. ACI (ACI) has an ICER of just under £18,000 (for a 20% increase in the duration of success rate for MF) and over £21,000 (for a 40% increase in the duration of success rate for MF). Note that for the 40% increase in the duration of the MF success, the difference in incremental QALYs between the two initial MF options is very small and hence the ICERs will fluctuate widely.

Figure 16 (a to b) presents the cost-effectiveness acceptability curves for the sensitivity analysis results for the 'what if' scenario if the duration of success of MF was to increase by 20% and 40%, respectively. For a 20% increase in the MF success rate, the graph suggests that if the decision maker is willing to pay £20,000 then there is not much difference in the four options; however, if the

decision maker is willing to pay £22,000 or more than ACI as a first repair is more cost-effective than MF as a first repair. For a 40% increase in the MF success rate, the graph indicates that if the decision maker is willing to pay £20,000 then ACI as a first repair (ACI (ACI) or ACI (MF)) is more cost-effective than MF (approximately 32-33% probability that it is more cost-effective).



a: Cost-effectiveness acceptability curves – increase in MF success rate by 20%



b: Cost-effectiveness acceptability curves – increase in MF success rate by 40%

Figure 16. Cost-effectiveness acceptability curves – increase in MF success rate

Note that MF only becomes cost-effective if the duration of benefit is much longer.

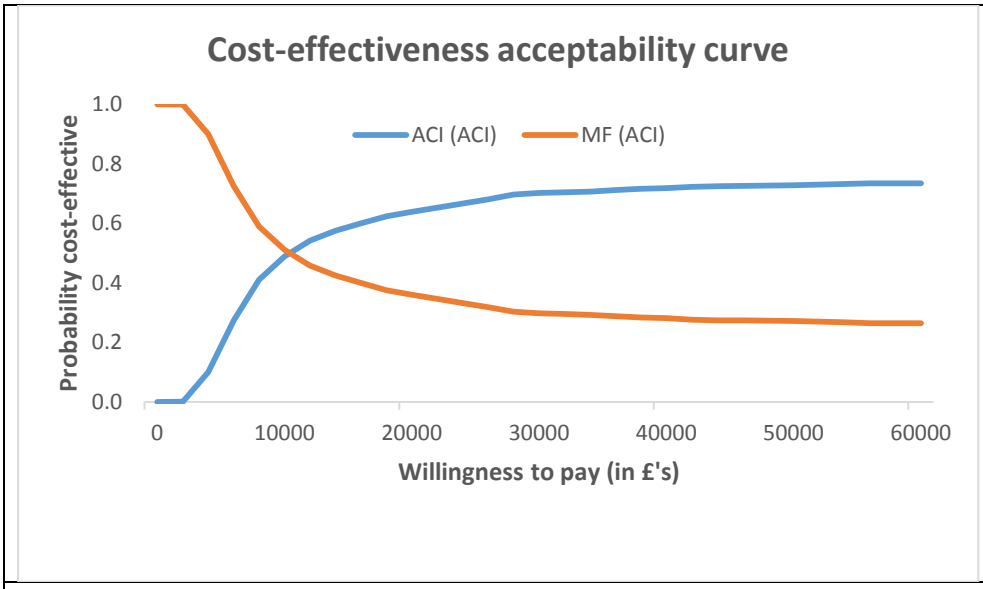
e) SA 5. Starting age of cohort is 45 years

In the base-case analysis the starting age for the cohort was 33 years. In this sensitivity analysis the starting age is changed to 45 years (patients are nearer to the knee replacement age) to see how this affects the incremental cost-effectiveness ratio. Table 26 presents the deterministic and probabilistic cost-effectiveness results by scenario. Even though the model is starting at a later age (45 years), the results are very similar to the base-case with ACI as a first repair being cost-effective compared with MF as a first repair.

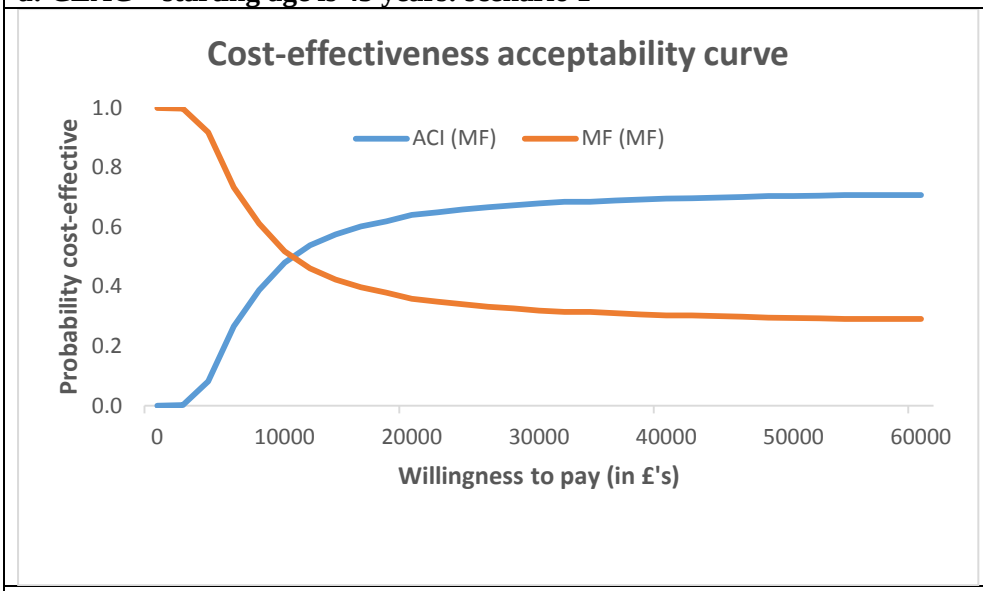
Table 26. Sensitivity cost-effectiveness results (by scenario) – starting age for cohort is 45 years

Procedure	Total mean costs £	Total mean QALYs	Incremental costs £	Incremental QALYs	ICER £ (cost per QALY gained)
Deterministic					
Scenario 1					
MF (ACI)	6,422	15.0445	-	-	-
ACI (ACI)	16,784	16.0327	10,362	0.9882	10,486
Scenario 2					
MF (MF)	5,267	15.0187	-	-	-
ACI (MF)	16,116	15.9766	10,849	0.9579	11,326
Probabilistic					
Scenario 1					
MF (ACI)	6,441	15.0833	-	-	-
ACI (ACI)	16,724	16.0377	10,283	0.9544	10,755
Scenario 2					
MF (MF)	5,281	14.9900	-	-	-
ACI (MF)	16,053	15.9562	10,772	0.9962	11,149

Figure 17 (a and b) presents the cost-effectiveness acceptability curves for the sensitivity analysis with a starting age of 45 years for the cohort for scenarios 1 and 2. For scenarios 1 and 2, if the decision maker was willing to pay £20,000, the probability that ACI was cost-effective relative to MF was 64%.



a: CEAC – starting age is 45 years: scenario 1



b: CEAC – starting age is 45 years: scenario 2

Figure 17. CEAC – starting age is 45 years

Table 27 shows the deterministic and probabilistic cost-effectiveness results with a starting age of 45 years for the cohort and results were ranked by the least costly option. Results were similar to the base-case results and ACI (ACI) remained the most cost-effective procedure.

Table 27. Sensitivity cost-effectiveness results – starting age for cohort is 45 years

Procedure	Total mean costs £	Total mean QALYs	Comparison	Incremental costs £	Incremental QALYs	ICER £ (cost per QALY gained)
Deterministic						
MF (MF)	5,267	15.0187	-	-	-	-
MF (ACI)	6,422	15.0445	MF (ACI) v MF (MF)	1,155	0.0258*	44,747
ACI (MF)	16,116	15.9766	ACI (MF) v MF (ACI)	9,695	0.9321	10,401
ACI (ACI)	16,784	16.0327	ACI (ACI) v ACI (MF)	667	0.0561*	11,898
Probabilistic						
MF (MF)	5,281	14.9900	-	-	-	-
MF (ACI)	6,441	15.0833	MF (ACI) v MF (MF)	1,160	0.0933*	12,439
ACI (MF)	16,053	15.9562	ACI (MF) v MF (ACI)	9,612	0.8729	11,012
ACI (ACI)	16,724	16.0377	ACI (ACI) v ACI (MF)	671	0.0815*	8,241

* As the incremental QALYs are near zero, the ICER can fluctuate widely

Figure 18 presents the cost-effectiveness acceptability curve for a starting age of 45 years for the cohort. If the decision maker is willing to pay £20,000 per QALY, then either ACI (ACI) or ACI (MF) are the most cost-effective options.

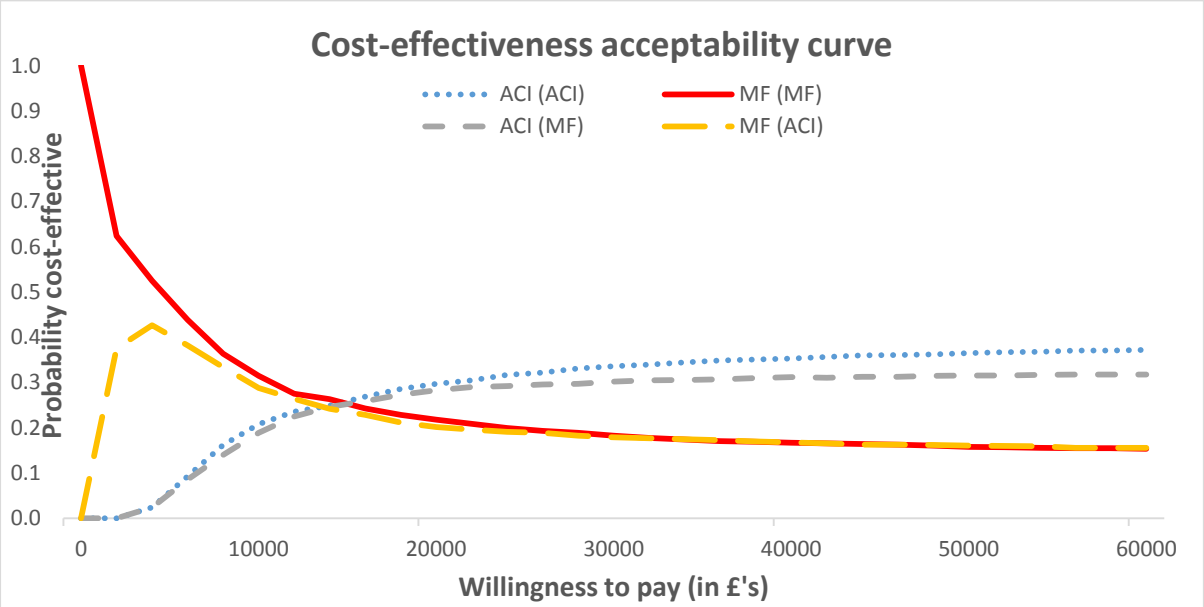
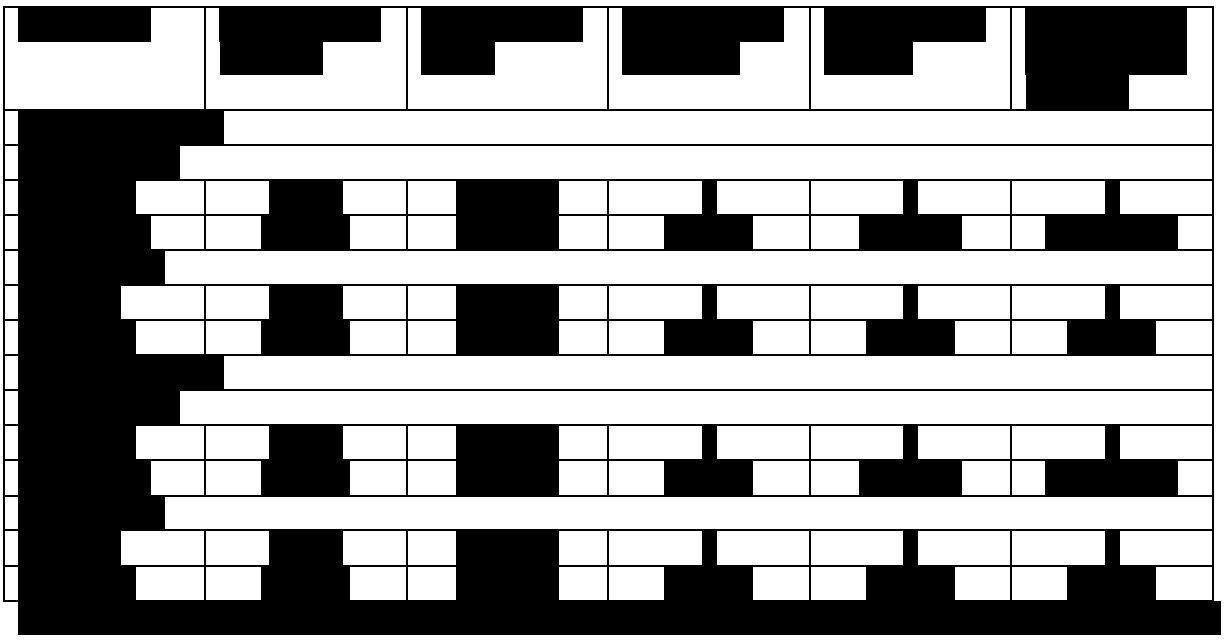


Figure 18. Cost-effectiveness acceptability curves – starting age of cohort is 45 years

[redacted]



[redacted]

[redacted]
[redacted]

[redacted]

[redacted] 29 [redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					

[redacted]

[redacted]

[redacted]

5.7 Discussion

For the base-case analysis, a hypothetical cohort of 1,000 patients with cartilage knee defects with a starting age of 33 years was followed over a lifetime horizon. The cycle length for the model was set to 1 year. The analysis was conducted from the perspective of the NHS and PSS. Data for the transition probabilities, mortality rates, and utilities were obtained from the literature. Health outcomes were measured in quality-adjusted life years. The majority of unit costs were obtained from the NHS reference costs database and all costs are in pounds sterling (£) in 2012/2013 prices. Results were compared in two different ways for ACI and MF:

- Firstly, we used two scenarios: - scenario 1 with all second repairs ACI and scenario 2 with all second repairs MF.
- Secondly, all four options were ranked in order of increasing costs and any options (sequences) which were more expensive and less effective were excluded (simple dominance).

Results are expressed as incremental cost per QALY gained. An annual discount rate of 3.5% was applied to both costs and QALYs. We ran the model deterministically and probabilistically with 1,000 iterations. We undertook various sensitivity analyses. These bootstrapped iterations were used to construct the cost-effectiveness acceptability curves. The CEACs were presented using a willingness to pay threshold from £0 to £60,000.

5.7.1 Methods and summary of findings

For the base-case analysis, for the discounted deterministic results MF was the least costly option but had fewer QALYs, whereas ACI was the most expensive option but generated more QALYs.
For scenario 1, the cost per QALY gained for ACI compared with MF was £8,925 and for scenario 2, the cost per QALY gained £9,788. These results were confirmed by the CEACs: so if the decision maker is willing to pay £20,000 for a QALY, ACI is 56%-59% more likely to be cost-effective than MF. For both scenarios, ACI as a first repair appeared more cost-effective than MF as a first repair.

When looking at the different sequences (options), the initial ACI appears more cost-effective than initial MF and for those that need a second repair after the first ACI, this should also be another ACI. For the different sequences, the cost-effectiveness acceptability curve for the base-case results confirmed these results and showed that if the decision maker is willing to pay £18,000 or more for a QALY than ACI as a first procedure is more cost-effective than MF as a first procedure.

We found that the key cost driver was the cost of the cells for the ACI procedure, but over the time horizon, ACI is more beneficial (more gain in QALYs) and cost saving to the NHS (less people in need of a second repair or of a TKR).

A number of sensitivity analyses were undertaken to determine the cost-effectiveness of various options and the majority of results were in line with the base-case analysis. However, we found that the model was sensitive to the cost of cells - we know that these are not the true costs as the NHS receive confidential discounts from the manufacturers. This means that with the cell cost reduction ACI (ACI) is likely to be even more cost-effective than the base-case cost per QALY ratio which was presented. We also found that the model was sensitive to the time horizon, with a shorter time horizon - 10 years – the cost per QALY for the two initial ACI options rose to around £26,000, due to the costs of the ACI procedure occurring at the start and the benefits of ACI not being realised until much later, such as the reduced need for TKRs. When the time horizon was longer, the model results were in line with the base-case results. The sensitivity analyses conducted using Oswestry data found ACI not cost-effective compared with MF and mainly due to the lower utility value in the fourth year for ACI compared with MF. However, for reasons explained in Chapter 4 – there are a number of confounding factors that influence these utility values.

5.7.2 Strengths and limitations

The Markov model considers patients having a maximum of two knee repairs (any combination of MF and ACI) if they choose to, if the first repair fails and unlike other models the patients can have more than two knee revisions.

However, the model does have a number of limitations. Firstly, the length of follow-up we found in the trials published in the literature was too short and hence, there is no long-term data on the success and failure rates (including long-term benefits and adverse events) for each of these procedures and what the average age is for these patients when a TKR/PKR is required. However, results from the long-term ACTIVE trial (comparing ACI/MACI with standard treatments) and the TOPKAT trial (comparing total knee replacement with partial knee replacement)[124] will provide useful information with which to populate our economic model, although results will not be available until 2017 and 2019, respectively.

Secondly, due to the short follow up, we also found that there were no long-term data on utility values associated with each of these procedures. We have had to rely heavily on the literature and on a few studies in particular, such as Gerlier et al[102]. Also, we found no studies that mapped any of the

clinical measures such as Lysholm score or the KOOS score to either the EQ-5D or SF-6D to generate utility values, which would have been helpful in our model.

Thirdly, we relied on our clinical experts to provide us with information on the average number of resources used (e.g. outpatient and rehabilitation visits) over the course of the year for these patients.

Fourthly, we did not take into account any costs for the analgesics based on advice from our clinical experts, as these costs are negligible and would not have altered the base-case cost per QALY. Also, not all the costs obtained were from the NHS reference costs. We used the previous HTA report by Clar et al[3] who obtained costs from Aberdeen/Southampton hospitals to populate their economic model. Although these costs were inflated to 2012/2013 prices using the Hospital and Community Health Services (HCHS) index,[114] to get a more accurate picture of these costs it would have been better to have carried out "bottom-up costing".

Fifthly, the model has not taken into account any private patient costs such as time off work and loss of pay (productivity) – this population who have either an ACI or MF is a young cohort and it will primarily have an effect on their own costs. In line with this, it would have been interesting to know how long it would take this population cohort to return to normal activities after each of these procedures (return to work or return to sports).

Finally, we did not include any adverse events as there were no key differences between the two treatment arms.

6 Chapter 6 Discussion

Statement of principal findings

- ACI has evolved since the last review by NICE in 2005, and key features now are selection of the chondrocytes most likely to produce good quality repairs ("characterization") and the use of chondrocytes seeded into membranes or scaffolds, rather than a liquid suspension of cells being secured under a periosteal or collagen cap.
- ACI is an effective way of treating defects in articular cartilage, giving good results in over 80% of patients. If results are good at two years, benefit is generally sustained for up to 10 years. A very large UK cohort showed graft survivals of 78% at 5 years and 51% at 10 years.
- The main comparator, microfracture, is also effective, but in a smaller proportion, and appears to be less durable. [redacted]
- Our economic modelling found that ACI appeared to be cost-effective compared to microfracture, with a key driver being duration of benefit and likely avoidance or postponement of a second repair or of knee replacement. MF was less costly but provided fewer QALYs.
- Total costs were influenced by the proportion needing a second repair, and by the method used for second repairs. If all second repairs were by ACI, the cost per QALY gained for initial ACI compared with initial MF was £8,925. If all second repairs were by MF, the cost per QALY gained was £9,788. These results were confirmed by the CEACs: so if the decision maker is willing to pay £20,000 for a QALY, ACI is 56%-59% more likely to be cost-effective than MF. For both scenarios, ACI as a first repair was more cost-effective than MF as a first repair. [redacted]

Strengths and weakness of evidence

- At the last appraisal, there was no long-term data from trials. The evidence base has also evolved with data on longer term follow-up both from trials and cohort studies. However the longest term data comes from older generations of ACI, and recruits to such studies had often had several prior attempts at repair which appears to reduce the effectiveness of ACI.

- Because of short follow-up of the MACI trials, there is a lack of long-term utility data.
- The TIG/ACT trial of ChondroCelect used ACI-P which has now been superseded by ACI-C or MACI. ChondroCelect cells are now used in a MACI procedure wherein the cells are loaded on to a membrane by the surgeon.
- [redacted]There is a general problem when long-term results are needed but the technology continues to evolve. Data on long-term results comes mainly from first generation ACI.
- Utilities vary considerably amongst studies. For example, baseline utility before repair ranges from 0.41 (Derret et al[101]) to [redacted] (ACTIVE[33], MF and ACI groups respectively) to 0.654 (Gerlier et al [102]).

Asymptomatic lesions.

[redacted]. Many will become asymptomatic and will no longer quality for ACI according to the NICE scope. However, their cartilage defect will not recover spontaneously, and they are likely to develop OA in later years. Should they be considered for ACI?

The Dutch Orthopaedic Association recommends treatment of asymptomatic ICRS grade 5 lesions.[20]

Osteoarthritis

The NICE scope excludes people with "advanced osteoarthritis". Osteoarthritis can be defined as generalised degenerative change affecting both sides of an articulation. ACI is used for isolated cartilage defects. There can be isolated defects on both surfaces ("kissing lesions") which could be considered for ACI if the rest of the joint is in good order, but our searches have found only trials in single defects. There is sparse evidence on the use of ACI in knees with osteophytes (which are a response to degenerative change). It is possible that ACI may have a place in early OA with focal damage. Minas and colleagues[125] carried out ACI-P in 153 patients with an average age of 38. Five years after ACI, 92% of patients had good function, and only 8% had had TKR.

Niemeyer and colleagues reported a case series of MACI (CartiGro cells and Chondro-Gide collagen membrane) in which some patients had early OA.[57] Their results were not as good as those in patients

without OA, but 73% (11/15) of them had improved function (increase in 10 points or more in IKDC) at 24 months.

The trials described in detail in this report provide little data on the value of ACI in OA. In the ACTIVE and Basad trials, patients with OA were excluded. In the SUMMIT trial, patients with Kellgren-Lawrence grade 3 or 4 OA were excluded, which implies that some patients with early OA (grade 2 has definite osteophytes and possible joint space narrowing) could have been included. However no details for such a sub-group are given in the results. In the TIG/ACT trial, patients with advanced OA (as defined by Radiographic Atlas OA grade 2 – 3) were excluded.

A systematic review of cartilage repair in early OA by de Windt et al[126] found evidence of benefit in those having various forms of ACI, ranging from ACI-P to MACI. Early OA was defined in different ways in the nine case series, and de Windt and colleagues described the studies as being of "generally low methodological quality". Nevertheless they reported that outcomes to 9 years were good, suggested that ACI in early OA might be used to postpone TKR, but recommended an RCT.

There may therefore be a place for ACI in early osteoarthritis but the evidence base is much weaker than for purely chondral lesions.

Body mass index

Jaiswal and colleagues from Stanmore reported a lack of benefit from ACI or MACI in patients with BMI over 30, though this was based on small numbers in the high BMI group.[127] Their data came from the trial of MACI versus ACI. In 53 patients with BMI under 25kg/m^2 82% of patients had a good or excellent result. In the overweight group (BMI 25-30) 49% (22 of 45) had a good or excellent result, whereas only one of 18 patients with BMI over 30 had a good result.

Mithoefer et al also reported worse outcomes in those with BMI over 30.[79] Behery et al reported no correlation but had data on only 8 patients.[80]

Data in the effect of high BMI on outcomes of cartilage repair is sparse. Jaiswal and colleagues reported that their literature review found few previous studies.[127] In most studies, mean BMIs were well below 30, perhaps because cartilage injuries occur largely in people active in sports. Jaiswal used the term "obese" but some sportsmen with high BMIs may be lean but very muscular.

Similar findings have been reported for microfracture by Asik and colleagues with better results in those with BMI less than 25.[128]

Research needs

Recommendations for research made in the systematic reviews.

Some of the recommendations made in the reviews are now out of date. Other recommendations include:

- High quality clinical trials are needed, fulfilling the following criteria:
  - Multicentre, adequate sample size with long term follow-up (preferably five to ten years)
  - Patients in trials should be stratified based on body mass index, defect location, post-debridement defect size and previous cartilage repair
  - Transparent patient enrolment with clearly stated inclusion and exclusion criteria
  - Proper independently performed randomisation techniques
  - No concurrent surgical interventions (anterior cruciate ligament reconstruction, realignment osteotomy, meniscal surgery, etc.); consistent surgical technique
  - Use of validated, responsive, and reliable patient-oriented outcome measures; clear reporting of data with a statement of both clinical relevance and significance; use of independent assessors
  - Further information is needed on the relationship between clinical, histological and radiological outcomes, and the most appropriate measure of functional outcomes that relate to a generic measure of health-related quality of life
- Cohort studies of long term effects ($\geq$10 years) are needed
- Research is needed to explain lack of return to sports by some patients
- Prospective long term studies are needed to determine if articular cartilage repair in athletes can influence the high incidence of osteoarthritis associated with high impact sports
- More studies should be done on the maturation process of finally formed repair tissue and on appropriate rehabilitation programmes for the different techniques

Fourth generation ACI

There are several lines of investigation.

Mesenchymal cells

It has been suggested that mesenchymal stem cells from bone marrow can be used as an alternative to ACI and that their reproduction is less affected by age. (For reviews see Nakamura et al[129] and Perera et al[130])

A review of scaffold-based repair by Filardo and colleagues[131] mentions another option, using mesenchymal stem cells and a degradable scaffold, covered with fibrin.[132]

The ASCOT trial will compare repairs with chondrocytes and bone marrow mesenchymal stem cells, and with the combination of both.[133]

INSTRUCT

This appears to be a one-stage procedure mixing chondrocytes and bone marrow cells, without cell culture. Cells from a biopsy of cartilage are mixed with bone marrow cells, then seeded into a porous scaffold which is then implanted into the defect. Evidence comes from a poster by Hendriks and colleagues.[134] So far only 37 patients had reached 12-month follow-up, of whom 72% had hyaline cartilage on biopsy.

Cartilage implantation

The development here is that instead of implanting cultured chondrocytes into the defect, the autologous chondrocytes are used to grow new cartilage in the laboratory which is then implanted.[135]

Gell-type ACI

Gell-type ACI appears to be a new variant without using membrane or periosteum, but using cells held in place with fibrin. Choi and colleagues report a case series with 98 patients.[136] There do not appear to have been RCs against standard ACI.

Single stage procedures

Cole and colleagues report an RCT with 29 patients, comparing MF (9 patients) with a cartilage autograft implantation system (CAIS) in which chondrocytes are not sent for culture.[86] Instead, hyaline cartilage is harvested in similar amount as for traditional ACI, but then minced and attached to a biodegradable scaffold with fibrin glue, in a single operation. Results at 24 months showed some advantages for the CAIS group, with IKDC score 83 for CAIS and 60 for MF, and KOOS scores also better.

Other cells

Mizuno et al report that ear cartilage cells can be used, at least in dogs.[137]

New forms of microfracture

Filardo and colleagues report 5 case series of autologous matrix-induced chondrogenesis which combines microfracture with a collagen matrix to stabilise the blood clot.[131] Long-term results are not yet available.

Siclari and colleagues used a combination of microfracture and a cell-free hyaluronan cap that had been immersed in autologous plasma in 52 patients.[138] At 2 years, KOOS results showed good improvement. Biopsies were taken from four patients and showed hyaline or hyaline-like repair tissue.

Metal or plastic patches for knees

These were excluded by NICE as comparators, but sound sufficiently promising to be used in trials. They may not be suitable for younger patients but might be an option for the 40-60 subgroup, perhaps in order to postpone knee replacement.

The HemiCap is used for re-surfacing localize damage in femoral condyles, and is described by the manufacturer as a "contoured articular resurfacing implant", and as "bridging the gap between biological therapies and TKR". The evidence base seems to consist of a few case series with no RCTs. It is produced by Arthrosurface®.[139]

- Patello Femoral HemiCAP®[140]
- UniCAP®[141]
- HemiCAP® Classic[142]

The BioPoly™ RS Knee System[143] is CE marked for sale in the EU. It is a hyaluronic and polythene implant for repairing the joint surface.

The Episealer (Episurf, Sockholm[144] comes in two forms, for femoral condyle and trochlea and is described as a small metallic button with implants tailored for each patient. It was due to be launched on 2013/14.

These products are said to allow rapid return to activities, unlike the long rehab required after ACI. A recent study reported that some sportspeople who had had ACI or MF followed by a long period of rehabilitation, did not regain full quadriceps power in 33% of individuals after MF and 26% after ACI.[145] Another reported good results after ACI-P with 26 of 33 patients have good or excellent results at 10 years, but also noted that patients did not return to full pre-injury activity levels.[146] This may be partly due to the long lay-off during the rehabilitation process. However those who return to previous activity too early have poorer outcomes than those who wait at least 12 months.[147]

Conclusion

The evidence base for ACI has improved since the last appraisal by NICE. In most analyses, the ICERs for ACI compared to microfracture appear to be within a range usually considered acceptable.

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142. Arthrosurface®. Femoral Condyle Implants. 2014 [cited 25/11/2014]; Available from: http://www.arthrosurface.com/products/knee/femoral-condyle-implants-intl-only/.
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8 Appendices

Appendix I. Flow diagram systematic review

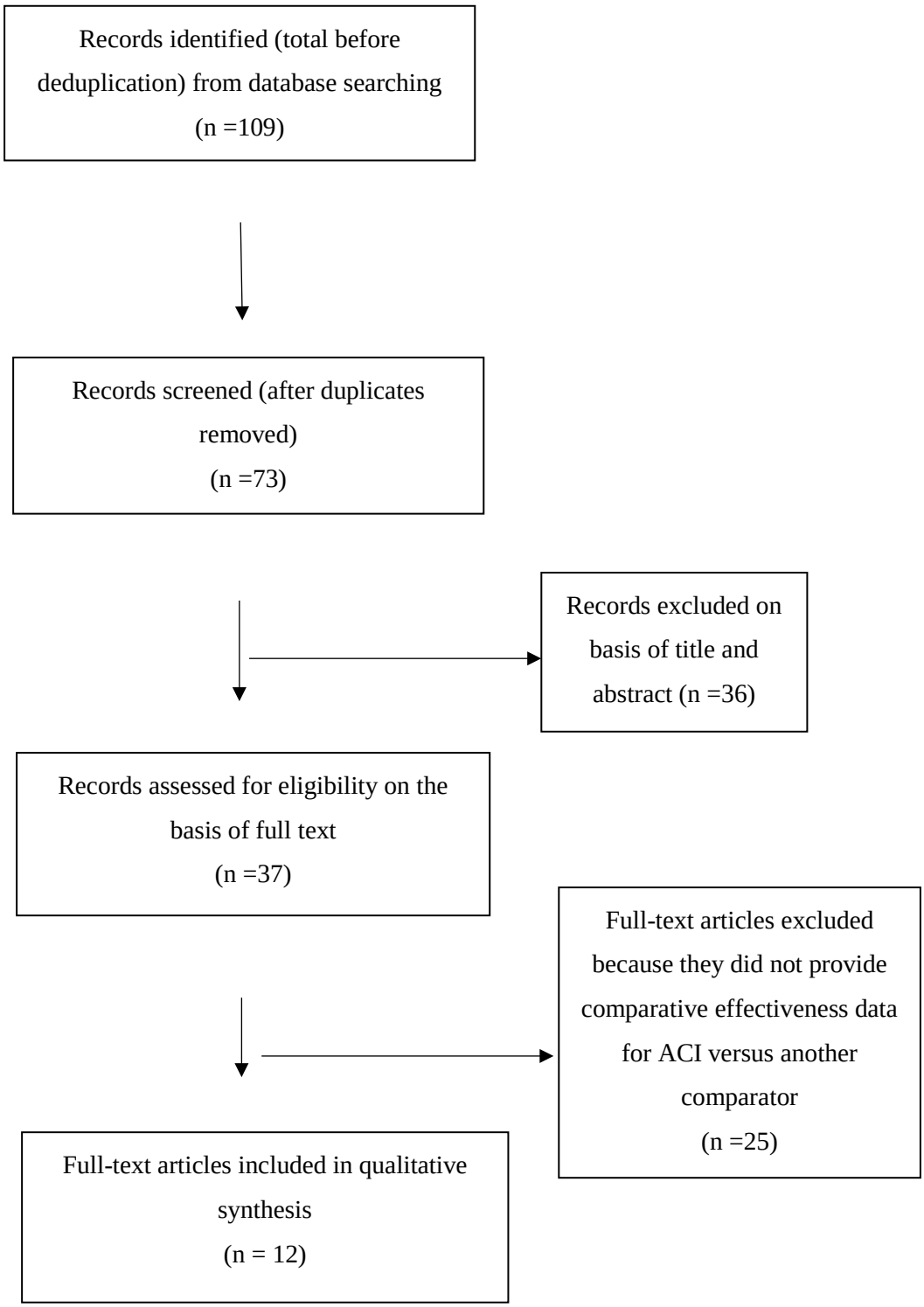


Figure 20. PRISMA study flow diagram for searches for systematic reviews

Appendix II. Search strategies for systematic review and primary studies

Searches for Systematic Reviews and Assessment Reports

Cochrane Database of Systematic Reviews : Issue 6 of 12, June 2014

(autologous chondrocyte* near/3 (implant* or transplant*))

Ovid MEDLINE(R) 1946 to June 17, 2014

1. exp Chondrocytes/tr [Transplantation]
2. exp Cartilage, Articular/tr [Transplantation]
3. exp Transplantation, Autologous/
4. (MACI or MACT or chondrocelect or ACI).tw.
5. (chondrocyte* adj4 (implant* or transplant* or matrix or characteri*)).tw.
6. (autologous adj3 (implant* or transplant* or chondrocyte* or cartilage)).tw.
7. (cartilage* adj2 (transplant* or implant*)).tw.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. (systematic review or meta-analysis).tw.
10. meta-analysis.pt.
11. "cochrane database of systematic reviews".jn.
12. 9 or 10 or 11
13. 8 and 12
14. limit 13 to yr="2004 -Current"
15. knee*.af.
16. 14 and 15

Embase 1980 to June 17, 2014

1. exp *chondrocyte implantation/
2. (MACI or MACT or chondrocelect or ACI).tw.
3. (chondrocyte* adj4 (implant* or transplant* or matrix or characteri*)).tw.
4. (autologous adj3 (implant* or transplant* or chondrocyte* or cartilage)).tw.
5. (cartilage* adj2 (transplant* or implant*)).tw.
6. 1 or 2 or 3 or 4 or 5
7. knee*.af.
8. 6 and 7
9. limit 8 to yr="2004 -Current"
10. (systematic review or meta-analysis).tw.
11. 9 and 10

Health Technology and other assessment reports

Searched the website of the CRD HTA database at http://www.crd.york.ac.uk/CRDWeb/HomePage.asp and the European Medicines Association (EMA), the US *Food and Drug Administration (FDA).*

Searches for primary studies for clinical effectiveness

Cochrane Central Register of Controlled Trials, Issue 6 of 12, June, 2014

(autologous chondrocyte* near/3 (implant* or transplant*))

Ovid MEDLINE(R) *1946 to June 17, 2014*

1. exp Chondrocytes/tr [Transplantation]
2. exp Cartilage, Articular/tr [Transplantation]
3. exp Transplantation, Autologous/
4. (MACI or MACT or chondrocelect or ACI).tw.
5. (chondrocyte* adj4 (implant* or transplant* or matrix or characteri*)).tw.
6. (autologous adj3 (implant* or transplant* or chondrocyte* or cartilage)).tw.
7. (cartilage* adj2 (transplant* or implant*)).tw.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. Knee/ or knee*.mp.
10. 8 and 9
11. limit 10 to yr="2010 -Current"
12. Animals/
13. Humans/
14. 12 not 13
15. 11 not 14

Embase *1947 to 2014 June 17*

1. exp *chondrocyte implantation/
2. (MACI or MACT or chondrocelect or ACI).tw.
3. (chondrocyte* adj4 (implant* or transplant* or matrix or characteri*)).tw.
4. (autologous adj3 (implant* or transplant* or chondrocyte* or cartilage)).tw.
5. (cartilage* adj2 (transplant* or implant*)).tw.
6. 1 or 2 or 3 or 4 or 5
7. exp knee/
8. knee*.tw.
9. 7 or 8
10. 6 and 9
11. limit 10 to yr="2010 -Current"
12. (rat or rats or pig or pigs or porcine or mice or murine or mouse or sheep or rabbit* or canine or dog*).ti.
13. 11 not 12

*Web of Science Core Collection***:** 2010-June 2014

TITLE: (("autologous chondrocyte" or "autologous cartilage") and (implant* or transplant*)) *AND* TOPIC: (knee*)

TITLE: (MACI or MACT or ACI or condrocelect or "characteri* chondrocyte*") *AND* TOPIC: (knee*)

Additional searches for other literature

Societies with meetings abstracts available online

- ISAKOS: International Society of Arthroscopy Knee Surgery & Orthopaedic Sports Medicine Biennial Congress 2013 https://www.isakos.com/
- AAOS: American Academy of Orthopaedic Surgeons annual meeting http://www.aaos.org/Annual
- ORS: Orthopaedic Research Society from 1999 to 2014 http://www.ors.org/abstract-search/
- AOSSM: American Orthopaedic Society for Sports Medicine 2013 Annual Meeting http://www.sportsmed.org/
- British Association for the Surgery of the Knee 2013 abstracts http://professional.baskonline.com/content/BASKCurrent.aspx

Searches for Guidelines

NHS Evidence http://www.evidence.nhs.uk/

British Orthopaedic Association http://www.boa.ac.uk/

British Association for the Surgery of the Knee http://www.baskonline.com/

Ongoing or recently completed studies searched on October 3rd, 20104

1. ClinicalTrials.gov http://clinicaltrials.gov/
2. WHO (World Health Organization) Clinical Trials Registry Platform Search Portal http://apps.who.int/trialsearch/Default.aspx
3. Current Controlled Trials http://www.controlled-trials.com/
4. UK Clinical Trials Gateway http://www.ukctg.nihr.ac.uk/default.aspx
5. EU Clinical Trials Register website https://www.clinicaltrialsregister.eu/
6. UK Clinical Research Network Study Portfolio http://public.ukcrn.org.uk/search/
7. EUDRACT European Clinical Trials Database https://eudract.ema.europa.eu/

Additional searches

In addition, the inclusion lists of recent systematic reviews were checked and experts contacted for unpublished data.

In addition, the reference lists of recent relevant systematic reviews will be checked and experts will be contacted for unpublished data.

Auto-alerts in Medline and Embase were run for the duration of the review to ensure that newly published studies were identified.

Appendix III. Quality assessment of reviews

Methodology and quality

The majority of reviews was rated as at least medium quality, with three reviews being rated as low quality [Goyal 2013 A[44] and B[45], Naveen 2012[46]], six reviews rated as medium quality [Bekkers 2009[47], Kon 2009[48], Magnussen 2008[49], Mithöfer 2009[50], Nakamura 2009[51], Negrin 2013[5]] and three reviews rated as high quality [Harris 2010[41], Vasiliadis 2010[42], Vavken 2010[53]].

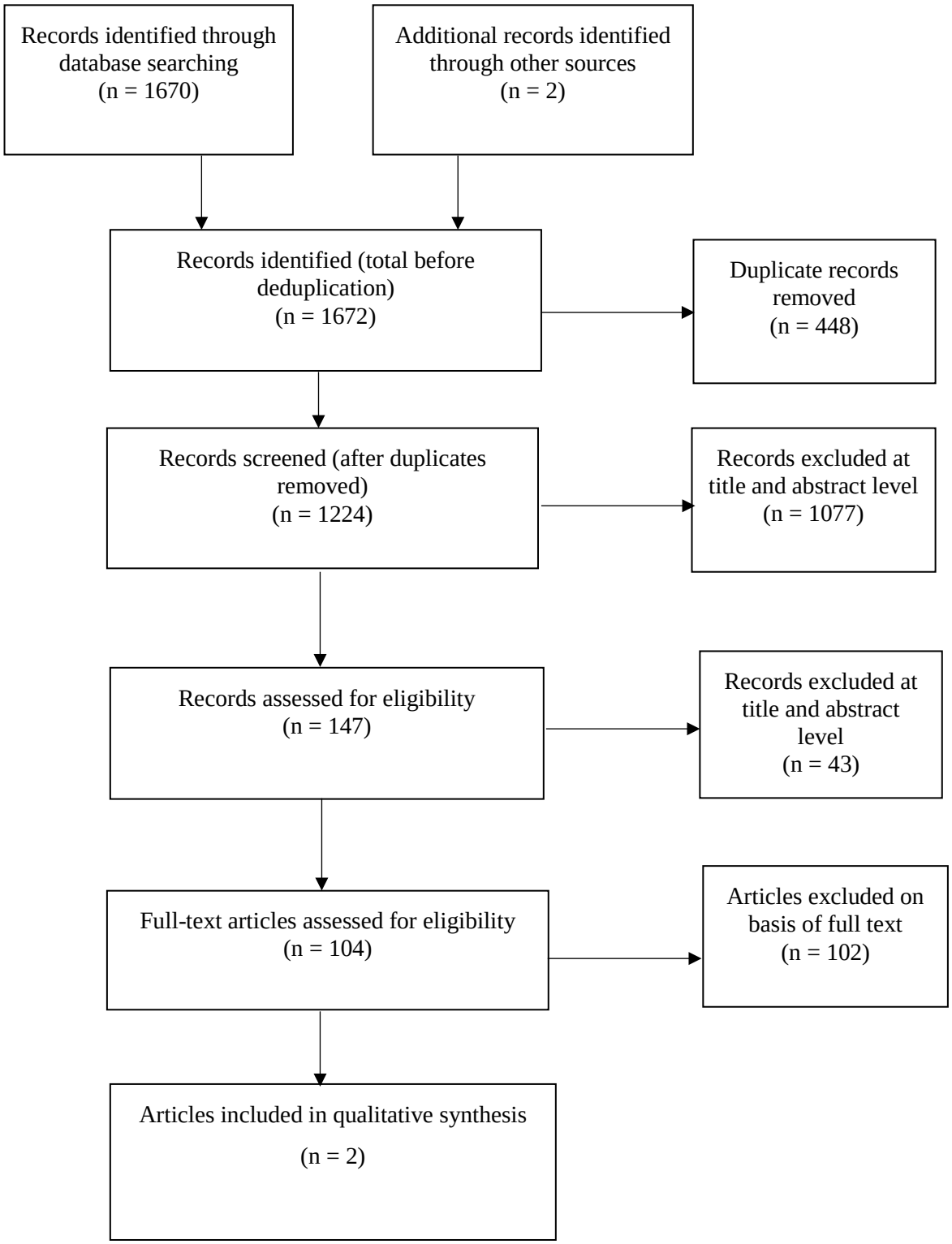
Ten of the 12 studies had an adequate description of inclusion criteria, two [Goyal 2013 A and B] had no adequate description of participants and outcome measures. Only one review was rated as having a fully adequate search strategy [Harris 2010]; search limitations included: only PubMed/Medline used [Goyal 2013 A and B, Nakamura 2009], English studies only included [Goyal 2013 A and B, Kon 2009, Magnussen 2008, Mithöfer 2009, Nakamura 2009], limited search terms (limited description or only few terms used) [Goyal 2013 A and B, Nakamura 2009, Naveen 2012, Negrin 2013, Vavken 2010], no additional searches mentioned [Bekker 2009, Goyal 2013 A and B, Nakamura 2009, Naveen 2012, Negrin 2013].

Study selection was only adequately described by four reviews [Harris 2010, Nakamura 2009, Negrin 2013, Vasiliadis 2010]; where described, selection was done by independent reviewers. Study flow was adequately shown (or described) by seven reviews [Goyal 2013A and B, Harris 2010, Magnussen 2008, Naveen 2012, Negrin 2013, Vavken 2010]. Quality assessment was adequately described by eight reviews [Bekkers 2009, Harris 2010, Kon 2009, Mithöfer 2009, Nakamura 2009, Negrin 2013, Vasiliadis 2010, Vavken 2010]; quality assessment tools included the Cochrane risk of bias tool [Bekkers 2009, Negrin 2013, Vasiliadis 2010], the Coleman Methodology Score (modified in some cases) [Bekkers 2009, Harris 2010, Kon 2009, Magnussen 2008, Mithöfer 2009], the Delphi list [Harris 2010], the rating system of the Journal of Bone and Joint Surgery plus Cochrane criteria [Nakamura 2009], a quality scale for observational studies by Deeks [Negrin 2013], and an unnamed list of quality items [Vavken 2010]. One review used quality as a basis for further selection [Bekkers 2009]. Items for data extraction were listed by eight reviews [Bekkers 2009, Harris 2010, Kon 2009, Magnussen 2008, Mithöfer 2009, Naveen 2012, Vasiliadis 2010, Vavken 2010], data extraction was done in duplicate by independent reviewers in five reviews [Kon 2009, Nakamura 2009, Negrin 2013, Vasiliadis 2010, Vavken 2010]. Most reviews did not include a meta-analysis and data were summarised in text and tables. A meta-analysis was included in the review by Negrin 2013 and the

Cochrane review by Vasiliadis 2010. Some reviews looked for patient characteristics related to treatment outcome.

All studies described the characteristics of included studies at least to some extent – but a number of reviews did not give details of the quality of individual studies [Goyal 2013A and B, Kon 2009, Negrin 2013]. All reviews showed the results of individual studies – but this was sometimes limited and numerical data were not always reported.

Appendix IV. PRISMA study flow diagram



Appendix V. Autologous chondrocyte implantation

BMSC: bone marrow-derived mesenchymal stem cell; C-ACI: collagen-based ACI; P-ACI: periosteum-based ACI; MACI: matrix-assisted autologous chondrocyte implantation

Table 30. Primary prospective comparative studies in reviews and from extra searches [this table shows publications belonging together and referring to the same study population]

	Bekkers 2009 Am J Sports Med 37: 1496	**Goyal 2013A** Athroscopy 29: 1872	**Goyal 2013B** Athroscopy 29: 1579	**Harris 2010** J Bone Joint Surg Am 92: 2220	**Kon 2009** Am J Sports Med 37 (Suppl 1): 156S	**Magnussen 2008** Clin Orthop Relat Res 466: 952	**Mithöfer 2009** Am J Sports Med 37 (Suppl 1): 167S	**Nakamura 2009** J Arthosc Relat Surg 25: 524	**Naveen 2012** Eur J Orthop Surg Traumatol 22: 89	**Negrin 2013** J Orthop Sci 18: 940	**Vasiliadis 2010** Knee Surg Sports Traumatol Arthrosc 18: 1645	**Vavken 2010** Osteoarth Cartilage 19: 957	**New**
C-ACI vs P-ACI													
RCT													
Gooding 2006 [21]		✓		✓				✓			✓		
ACI vs MACI													
RCTs													
Bartlett 2005[54]		✓		✓	✓	✓		✓			✓		
Zeifang 2010 [55]		✓		✓					✓				
Comparative cohort													
Erggelet 2009[56]									✓				
Niemeyer 2008[57]									✓				
Open vs arthroscopic ACI													
Comparative cohort / CCT													
Ferruzzi 2008[58]				✓	✓								
ACI vs													

	Bekkers 2009 Am J Sports Med 37: 1496	**Goyal 2013A** Athroscopy 29: 1872	**Goyal 2013B** Athroscopy 29: 1579	**Harris 2010** J Bone Joint Surg Am 92: 2220	**Kon 2009** Am J Sports Med 37 (Suppl 1): 156S	**Magnussen 2008** Clin Orthop Relat Res 466: 952	**Mithöfer 2009** Am J Sports Med 37 (Suppl 1): 167S	**Nakamura 2009** J Arthosc Relat Surg 25: 521	**Naveen 2012** Eur J Orthop Surg Traumatol 22: 89	**Negrin 2013** J Orthop Sci 18: 940	**Vasiliadis 2010** Knee Surg Sports Traumatol Arthrosc 18: 1645	**Vavken 2010** Osteoarth Cartilage 18: 857	**New**
mosaicplasty													
RCT													
Bentley 2003[4]	✓					✓		✓	✓		✓	✓	
Dozin 2005 [59]				✓				✓	✓		✓	✓	
CCT													
Horas 2000[601] **Horas 2003** [5]				✓		✓		✓	✓		✓	✓	
ACI vs microfracture													
RCT													
Basad 2004[7] **Basad 2010**[61] **Bachmann 2004**[62]			✓	✓	✓				✓	✓	✓	✓	
Crawford 2012[63]										✓			
Knutsen 2004[6] **Knutsen 2007**[64]	✓		✓	✓		✓		✓	✓	✓	✓	✓	
Lim 2012[65]			✓										
Saris 2008[66] RCT **Saris 2009**[67] **Vanlauwe 2011**[40] **Van Assche 2009**[68] **Van Assche 2010**[69]	✓		✓	✓			✓	✓	✓	✓	✓	✓	

[1] Described as RCT but inadequate randomisation method (alternation)

	Bekkers 2009 Am J Sports Med 37: 149[illegible]	**Goyal 2013A** Athroscopy 29: 1872	**Goyal 2013B** Athroscopy 29: 1579	**Harris 2010** J Bone Joint Surg Am 92: 2220	**Kon 2009** Am J Sports Med 37 (Suppl 1): 156[illegible]	**Magnussen 2008** Clin Orthop Relat Res 466: 952	**Mithöfer 2009** Am J Sports Med 37 (Suppl 1): 167[illegible]	**Nakamura 2009** J Arthosc Relat Surg 25: 521	**Naveen 2012** Eur J Orthop Surg Traumatol 22: 89	**Negrin 2013** J Orthop Sci 18: 940	**Vasiliadis 2010** Knee Surg Sports Traumatol Arthrosc 18: 1645	**Vavken 2010** Osteoarth Cartilage 18: 857	**New**
Comparative cohort													
Kon 2009A[70] Am J Sports Med 37: 33			✓	✓	✓	✓	✓	✓	✓	✓			
Kon 2011[71]			✓							✓			
Minas 2009[72]									✓				
ACI vs BMSC													
Comparative cohort													
Nejadnik 2010[73]									✓				
ACI vs abrasionplasty													
RCT													
Visna 2004[74]					✓	✓		✓	✓		✓	✓	

Appendix VI. Characteristics of systematic reviews

Table 31. Characteristics and quality of systematic reviews

Review	Inclusion criteria and methodology	Included studies	Quality
Bekkers 2009[47] **Focus:** to identify parameters for valid treatment selection in the repair of articular cartilage lesions of the knee **Funding:** not reported, but stated that the authors have no conflicts of interest	**INCLUSION CRITERIA** **Study design:** prospective randomised and quasi-randomised trials **Participants:** focal cartilage lesions of the knee **Intervention:** comparison of at least two of ACI, microfracture or osteochondral autologous transplantation **Outcomes:** not specified **METHODOLOGY** **Search strategy:** *databases:* PubMed, Embase, Cochrane Library CENTRAL; *date of search:* August 25 2009; keywords indicated; *limitations:* PubMed limited by title and abstract, articles in English, German, French or Dutch; *additional searches:* none **Study selection:** based on titles and abstracts, but not stated how many reviewers were involved **Quality assessment:** done by 2 independent reviewers, based on Cochrane risk of bias tool and Coleman Methodology Score; quality used as a basis for further	**Number of included trials:** 4 (3 including ACI, only these are considered here) **Number of participants:** 298 **TRIALS** **Design:** RCTs **Follow-up:** 19 months to 5 years **Quality:** only level of evidence 1b included; 1/3 studies had some selection, detection and reporting bias; Coleman score 74 to 94 **Origin:** NR **Funding:** NR **PARTICIPANTS** **Age:** 30.9 to 33.9 years **Sex:** 57 to 80% men **Defect size:** mean 2.4 to 5.1 cm^2 **Duration of symptoms:** NR **Other:** n=2 femoral condyles; n=1 53% medial femur, 25% patella, 18% lateral femur, 3% trochlea, 1% lateral tibia **INTERVENTIONS** n=2 ACI, n=1 characterised chondrocyte implantation; n=1 mosaicplasty, n=2 microfracture **OUTCOMES** Clinical outcomes (modified	**Inclusion criteria described/adequate:** yes **Literature search described/adequate:** partly, no additional searches **Study selection described/adequate:** no **Data extraction described/adequate:** yes **Study quality assessment described/adequate:** yes **Study flow shown:** partly, in the text **Study characteristics of individual studies described:** yes **Quality of individual studies given:** yes **Results of individual studies shown:** yes **Statistical analysis appropriate:** yes **OVERALL QUALITY: medium**

Review	Inclusion criteria and methodology	Included studies	Quality
	selection **Data extraction:** items extracted listed **Meta-analysis:** no **Data analysis:** text and tables **Subgroup/sensitivity analyses:** looked for indicators of treatment selection / patient profile	Cincinnati, KOOS, Lysholm, VAS, Tegner), SF-36, ICRS macroscopic grading, histology	
Goyal 2013A[44] **Focus:** to examine the level I and level II evidence for newer generations of ACI versus first generation ACI and to establish if the newer generations have overcome the limitations of first generation ACI **Funding:** not reported, but stated that the authors have no conflicts of interest	**INCLUSION CRITERIA** **Study design:** phase I or II RCTs, systematic reviews / meta-analyses, prospective cohort studies **Participants:** no criteria specified **Intervention:** comparison of newer methods of ACI (suspended cultured chondrocytes with covering of collagen membrane; procedures delivering ACI using cell carriers or cell-seeded scaffolds) **Outcomes:** no criteria specified **METHODOLOGY** **Search strategy:** *databases:* PubMed; *date of search:* Nov 2012; keywords listed (partially), including restriction by study type; *limitations:* past 10 years, English language; *additional searches:* not specified **Study selection:** methods not	**Number of included trials:** 7 (4 studies comparing interventions; 1 study comparing younger and older patients; 2 studies of rehabilitation); only first 4 studies considered here **Number of participants:** comparative intervention studies: 180 (only reported for 3 of 4 studies, range 21 to 91 per study (n=3)) **TRIALS** **Design:** comparative intervention studies: 3 RCTs, 1 cost-effectiveness study **Follow-up:** 1 to 2 years **Quality:** not reported; 2 trials referred to as level I and 2 as level II evidence **Origin:** NR **Funding:** NR **PARTICIPANTS** **Age:** mean age 29.3 to 33.7 years (reported by 3 RCTs) **Defect size:** mean 4.1 to 6 cm^2 (reported by 3 RCTs)	**Inclusion criteria described/adequate:** partially described; inadequate **Literature search described/adequate:** partially described; inadequate **Study selection described/adequate:** not described; inadequate **Data extraction described/adequate:** not described; inadequate **Study quality assessment described/adequate:** not described; inadequate **Study flow shown:** yes **Study characteristics of individual studies described:** yes, but limited **Quality of individual**

Review	Inclusion criteria and methodology	Included studies	Quality
	stated; flowchart shown **Quality assessment:** no quality assessment reported **Data extraction:** methods not stated **Meta-analysis:** no **Data analysis:** text **Subgroup/sensitivity analyses:** none; comparisons described individually	No further details reported **INTERVENTIONS** periosteum-based ACI versus collagen-based ACI (n=2), periosteum-based ACI versus MACI (n=1), collagen-based ACI versus MACI (n=1) **OUTCOMES** Clinical and activity scores, cost-effectiveness, quality of life, MRI results	**studies given:** no **Results of individual studies shown:** yes**,** but limited **Statistical analysis appropriate:** NA **OVERALL QUALITY: low**
Goyal 2013B[45] **Focus:** to examine the level I and level II evidence for microfracture techniques for cartilage repair **Funding:** not reported, but stated that the authors have no conflicts of interest	**INCLUSION CRITERIA** **Study design:** phase I or II RCTs, systematic reviews / meta-analyses, prospective cohort studies **Participants:** no criteria specified **Intervention:** microfracture / marrow stimulation techniques **Outcomes:** no criteria specified **METHODOLOGY** **Search strategy:** *databases:* PubMed; *date of search:* Nov 2012; keywords listed (partially), including restriction by study type; *limitations:* past 10 years, English language; *additional searches:* not specified **Study selection:** methods not stated; flowchart shown **Quality assessment:** no quality assessment reported	**Number of included trials:** 15 (11 studies comparing with ACI, only these are considered here – counts separate papers as separate studies, probably just 6 separate study populations) **Number of participants:** 6 separate ACI study populations: 449 (range 41 to 118 per study) **TRIALS** **Design:** study types not clearly reported (n=4 RCTs, n=2 comparative cohort) **Follow-up:** 1.5 to 7.5 years **Quality:** not reported; 5/11 studies referred to as level I and 5/11 as level II evidence **Origin:** not reported **Funding:** not reported **PARTICIPANTS** **Age:** mean age 26.5 to 37.5 years (one study only reported range 18 to 45 years)	**Inclusion criteria described/adequate:** partially described; inadequate **Literature search described/adequate:** partially described; inadequate **Study selection described/adequate:** not described; inadequate **Data extraction described/adequate:** not described; inadequate **Study quality assessment described/adequate:** not described; inadequate **Study flow shown:** yes **Study characteristics of individual studies described:** yes

Review	Inclusion criteria and methodology	Included studies	Quality
	Data extraction: methods not stated **Meta-analysis:** no **Data analysis:** text and tables **Subgroup/sensitivity analyses:** none; comparisons described individually	**Sex:** unclear, only reported for microfracture group, more men than women **Defect size:** mean 1.9 to 2.8 cm^2 (2 studies only reported ranges 2 to 10 and 4 to 10 cm^2) **Duration of symptoms:** 1.6 to 3 years (reported by 3 studies) **INTERVENTIONS** ACI (n=1), characterised chondrocytes (n=2), MACI (n=1), scaffold-based ACI (n=2), periosteum-based ACI (n=1); all versus microfracture **OUTCOMES** Clinical and activity scores, histology	**Quality of individual studies given:** no **Results of individual studies shown:** yes **Statistical analysis appropriate:** NA **OVERALL QUALITY: low**
Harris 2010[41] **Focus:** effect of ACI versus other cartilage procedures on clinical outcomes, MRI, arthroscopic assessment, durability; effect of different generations of ACI and of patient- and defect-specific parameters **Funding:** no specific funding	**INCLUSION CRITERIA** **Study design:** level I and II evidence (RCTs with >80% FU; RCTs with <80% FU, prospective cohort studies); minimum duration of FU 12 months **Participants:** participants with Outerbridge/ICRS Grade-III or IV focal cartilage defects of the knee **Intervention:** (1) comparison of any generation ACI with any cartilage repair or restoration technique, (2) comparison of any generation ACI with a different generation of ACI, (3)	**Number of included trials:** 13 (but really just 10 distinct trial populations) **Number of participants:** 917 (700 distinct participants) **TRIALS** **Design:** n=6 level I, n=7 level II evidence (n=7 RCTs, n=3 CCT / comparative cohort) **Follow-up:** 1 to 5 years **Quality:** mean Coleman methodology score 54/100 (range 36 to 64), (n=7 fair, n=6 poor) **Origin:** not reported **Funding:** 4 studies declared	**Inclusion criteria described/adequate:** yes **Literature search described/adequate:** yes **Study selection described/adequate:** yes **Data extraction described/adequate:** partly; inadequate **Study quality assessment described/adequate:** yes **Study flow shown:** yes

Review	Inclusion criteria and methodology	Included studies	Quality
	evaluation of both arthroscopic and open arthrotomy ACI **Outcomes:** validated clinical outcome measures **METHODOLOGY** **Search strategy:** *databases:* Medline, Embase, Cinahl, PubMed, SPORTDiscus, Cochrane Library Systematic Reviews; *date of search:* latest search Feb 2010; keywords listed; *limitations:* no relevant limitations; *additional searches:* bibliographies of reviewed papers **Study selection:** independent search and selection by 4 reviewers, agreement by discussion or in case of persistent disagreement by the senior author **Quality assessment:** yes, Delphi list and modification of the Coleman methodology score **Data extraction:** details of extracted outcomes reported, but no details of methodology **Meta-analysis:** no **Data analysis:** tables and text; effect sizes calculated **Subgroup/sensitivity analyses:** data presented by comparator	a financial conflict of interest **PARTICIPANTS** **Age:** mean age 28.7 to 34.2 years **Sex:** NR **Defect size:** mean 1.9 to 6.2 cm^2 **Duration of symptoms:** 1.75 to 8.6 years **Other:** full thickness (100%) and isolated single defects (80 to 100%); median 88.5% (0 to 100%) had had previous surgery (reported by 10 studies) **INTERVENTIONS** n=604 ACI (497 distinct), n=271 microfracture (161 distinct), n=42 osteochondral autograft; ACI: n=4 open ACI 2nd generation (MACI), n=2 open periosteum cover characterised chondrocyte implantation (ChondroCelect), n=7 open periosteum cover ACI, n=2 arthroscopic ACI 2nd generation (Hyalograft C), n=2 open collagen membrane ACI **OUTCOMES** Clinical outcomes (Lysholm, Tegner, KOOS, ICRS, IKDC, modified Cincinnati), SF-36, histology / histomorphology	**Study characteristics of individual studies described:** yes **Quality of individual studies given:** yes **Results of individual studies shown:** yes **Statistical analysis appropriate:** yes **OVERALL QUALITY: high**

Review	Inclusion criteria and methodology	Included studies	Quality
Kon 2009[48] **Focus:** to summarise all studies related to the clinical application of MACI **Funding:** not reported; stated that the authors have no potential conflict of interest	**INCLUSION CRITERIA** **Study design:** any **Participants:** articular cartilage repair of the knee **Intervention:** second generation ACI, MACI **Outcomes:** 'clinical information' **METHODOLOGY** **Search strategy:** *databases:* Medline, Medline preprints, Embase, Cinahl, Life Science Citations, British National Library of Health, Cochrane CENTRAL; *date of search:* Jan 1 1995 to July 1 2008; keywords indicated; *limitations:* English language; *additional searches:* bibliographies of relevant studies and reviews **Study selection:** studies selected by 3 independent reviewers **Quality assessment:** modified Coleman Methodology Score **Data extraction:** data extracted by 3 independent reviewers; items extracted listed **Meta-analysis:** no **Data analysis:** text and tables **Subgroup/sensitivity analyses:** none	**Number of included trials:** 18 **Number of participants:** 731 (range 8 to 141) **TRIALS** **Design:** n=2 RCTs, n=3 prospective comparative (but 1 of these is an RCT), n=11 prospective cohort studies or case series, n=2 retrospective case series **Follow-up:** range 6.5 months to 5 years, median 2 years **Quality:** mean modified Coleman Methodological Score (of 100) 53.1 SD1.5 (range 33 to 82) **Origin:** NR **Funding:** NR **PARTICIPANTS** **Age:** mean age 26.4 to 37.6 years **Sex:** NR **Defect size:** mean 2.4 to 6.1 cm^2 **Duration of symptoms:** NR **Other:** n=334 cases traumatic lesions, n=236 degenerative, n=105 osteochondritis dissecans, n=56 other; 58% on medial femoral condyle, 17% lateral femoral condyle, 12% patella, 7% trochlea, 4% tibial plateau, 2% multiple areas; 63% had had previous surgery, 41% had	**Inclusion criteria described/adequate:** yes **Literature search described/adequate:** yes, but English only **Study selection described/adequate:** yes **Data extraction described/adequate:** yes **Study quality assessment described/adequate:** yes **Study flow shown:** no **Study characteristics of individual studies described:** yes **Quality of individual studies given:** no **Results of individual studies shown:** individual results plotted but studies not specified **Statistical analysis appropriate:** unclear, results of comparative studies not reported **OVERALL QUALITY: medium**

Review	Inclusion criteria and methodology	Included studies	Quality
		additional surgery **INTERVENTIONS** Only reported for ACI: n=9 Hyalograft C, n=1 BioSeed C, n=1 atelocollagen, n=1 BioCart II, n=4 MACI, n=1 Cartipatch, n=1 Chondrograft **OUTCOMES** Clinical outcomes (IKDC subjective, IKDC objective, Lysholm, Cincinnati; Tegner, ICRS subjective and functional, Stanmore, Meyers, VAS scales, KOOS), SF-36, EQ-5D	
Magnussen 2008[49] **Focus:** to determine whether ACI or osteochondral autograft transfer (OAT) results in better clinical outcomes compared with each other or with traditional abrasive treatment of isolated articular cartilage defects and to assess effects of lesion size on outcome **Funding:** authors have received funding from Vanderbilt Sports Medicine research fund,	**INCLUSION CRITERIA** **Study design:** level I and level II studies – prospective comparative studies; minimum 30 participants, minimum FU 1 year **Participants:** articular cartilage defects of the knee, full thickness lesions (Outerbridge Grade III or IV) **Intervention:** operative treatment with ACI or osteochondral autograft transfer compared to another method **Outcomes:** any clinical outcome measures **METHODOLOGY** **Search strategy:** *databases:* Medline, Cochrane Register of Controlled Trials, Embase,	**Number of included trials:** 6 (5 involving ACI, 1 trial of OAT vs microfracture not considered here) **Number of participants:** 361 (studies involving ACI, range 40 to 100) **TRIALS** **Design:** n=4 RCTs, n=1 CCT **Follow-up:** 1 to 2 years **Quality:** quality scores for each study not detailed; all included studies were subject to some degree of bias including selection bias, transfer bias, detection bias **Origin:** NR **Funding:** NR **PARTICIPANTS** **Age:** mean 30.8 to 33.5 years	**Inclusion criteria described/adequate:** yes **Literature search described/adequate:** yes, but English only **Study selection described/adequate:** no **Data extraction described/adequate:** partially **Study quality assessment described/adequate:** partially **Study flow shown:** yes, described in the text **Study characteristics of individual studies described:** yes

Review	Inclusion criteria and methodology	Included studies	Quality
National Institute of Arthritis and Musculoskeletal Skin Diseases and Pfizer Scholars Award in Epidemiology	Cinahl; *date of search:* Jan 1 1966 to Jan 1 2007; keywords listed, restricted by study type; *limitations:* English language; *additional searches:* bibliographies of included trials **Study selection:** methods not stated **Quality assessment:** modified Coleman methodology score **Data extraction:** predesigned form used and data extracted listed; no further methodology described **Meta-analysis:** no **Data analysis:** text and tables **Subgroup/sensitivity analyses:** none	**Sex:** NR **Defect size:** mean 3.72 to 6.1 cm^2 **Duration of symptoms:** 36 to 102.7 months (reported by 3 trials) **Other:** 43 to 100% traumatic lesions; 45 to 89% medial femoral condyle, 10 to 18% lateral femoral condyle, 0 to 32% patella, 0 to 13% trochlea, 0 to 8% tibial plateau; 1 trial reported cointerventions; time to full weightbearing 1 day to 12 weeks **INTERVENTIONS** Every trial examined a different comparison: C-ACI vs MACI, P-ACI vs microfracture, MACI vs abrasion, P-ACI or C-ACI vs open OAT, P-ACI vs open OAT **OUTCOMES** Clinical scoring systems (ICRS, VAS, Stanmore, Lysholm, IKDP, Tegner, Meyers, modified Cincinnati), arthroscopy, histology	**Quality of individual studies given:** not overall, but quality criteria described in the text **Results of individual studies shown:** yes **Statistical analysis appropriate:** NA **OVERALL QUALITY: medium**
Mithöfer 2009[50] **Focus:** to assess the effects of articular cartilage repair on athletic participation **Funding:** NR	**INCLUSION CRITERIA** **Study design:** RCTs, prospective and retrospective studies with or without a control group with FU data of ≥2 years; studies with macroscopic or histologic	**Number of included trials:** 20 (7 including ACI, with 6 distinct populations, only these are considered here) **Number of participants:** 535 distinct participants **TRIALS**	**Inclusion criteria described/adequate:** yes **Literature search described/adequate:** yes, but English only **Study selection**

Review	Inclusion criteria and methodology	Included studies	Quality
	data from second-look arthroscopy >12 months after surgery; FU >80% **Participants:** athletes with articular cartilage lesions (International Cartilage Repair Society grade III or IV chondral or osteochondral defects of the knee (femoral condyle, tibia, and patellofemoral)); ≥20 participants **Intervention:** articular cartilage repair **Outcomes:** sports activity-related functional outcome scores, ability to return to sports after surgery, ability to continue participation in athletic activity over time **METHODOLOGY** **Search strategy:** *databases:* Medline, Medline preprints, Embase, Cinahl, Life Science Citations, British National Library of Health (incl. Cochrane CENTRAL); *date of search:* 1966 to May 31 2009; keywords indicated; *limitations:* English language; *additional searches:* bibliographies of relevant studies and reviews; meeting abstracts **Study selection:** NR **Quality assessment:** modified Coleman	**Design:** n=1 RCT, n=1 comparative cohort, n=2 cohort without comparison group, n=2 case series **Follow-up:** 3 to 5 years **Quality:** Coleman Methodology Score 65 to 100; n=1 level 1 evidence, n=3 level 2 evidence, n=2 level 4 evidence **Origin:** NR **Funding:** NR **PARTICIPANTS** **Age:** overall 29 SE6 years; ACI 28 SE4 years **Sex:** NR **Defect size:** overall 3.6 SE0.4 cm^2; ACI 5.1 SE0.8 cm^2 **Duration of symptoms:** overall 21 SE3 months; ACI 23 SE 3 months **Other:** ACI: lesion type: single only 57%, single and multiple 43%; traumatic only 86%, traumatic and degenerative 14; lesion location: femorotibial only 29%, femorotibial and patellofemoral 71% **INTERVENTIONS** Of 20 studies, n=7 ACI, n=12 microfracture, n=5 OAT, n=1 allograft **OUTCOMES** Functional outcomes (KOOS, Tegner), return to sports	**described/adequate:** no **Data extraction described/adequate:** partly; inadequate **Study quality assessment described/adequate:** yes **Study flow shown:** partly in the text **Study characteristics of individual studies described:** yes **Quality of individual studies given:** yes **Results of individual studies shown:** yes **Statistical analysis appropriate:** yes **OVERALL QUALITY: medium**

Review	Inclusion criteria and methodology	Included studies	Quality
	Methodology Scores **Data extraction:** items extracted listed, no details of methodology **Meta-analysis:** no **Data analysis:** text, tables, correlations **Subgroup/sensitivity analyses:** analysis by comparison		
Nakamura 2009[51] **Focus:** to determine the effectiveness of cell-based therapy for articular cartilage defects of the knee **Funding:** ISAKOS Scientific Committee (presumably)	**INCLUSION CRITERIA** **Study design:** RCTS, prospective comparative studies, systematic reviews, case series **Participants:** symptomatic chondral lesions of the knee **Intervention:** cell-based therapies **Outcomes:** no criteria specified **METHODOLOGY** **Search strategy:** *databases:* Medline; *date of search:* 1994 to Jan 2009; keywords not indicated; *limitations:* English language; *additional searches:* none **Study selection:** independent selection by 3 reviewers, differences resolved by discussion **Quality assessment:** quality assessment according to the rating system of the Journal of Bone and Joint Surgery, supplemented by criteria of	**Number of included trials:** 12 (n=10 comparing interventions, n=2 regarding activity levels / rehabilitation), plus 3 systematic reviews – only 10 studies comparing interventions considered here (n=9 with distinct populations) **Number of participants:** 754 in intervention studies reported (really 674 distinct participants) **TRIALS** **Design:** n=9 RCTs, n=1 CCT **Follow-up:** 1 to 5 years **Quality:** n=2 RCTs classified as level I evidence, n=6 RCTs and n=1 CCT as level II evidence; quality limitations included lack of allocation concealment, not enough information on losses to follow-up and blinding **Origin:** NR	**Inclusion criteria described/adequate:** yes **Literature search described/adequate:** partly; inadequate **Study selection described/adequate:** yes **Data extraction described/adequate:** partly; inadequate **Study quality assessment described/adequate:** yes **Study flow shown:** no **Study characteristics of individual studies described:** yes **Quality of individual studies given:** yes **Results of individual studies shown:** yes **Statistical analysis appropriate:** NA **OVERALL QUALITY: medium**

Review	Inclusion criteria and methodology	Included studies	Quality
	the Cochrane Collaboration and Schulz 1995; data evaluated by reviewers independently, differences resolved by discussion **Data extraction:** data evaluated by reviewers independently, differences resolved by discussion **Meta-analysis:** no **Data analysis:** text and tables **Subgroup/sensitivity analyses:** data presented by comparator	**Funding:** NR **PARTICIPANTS** **Age:** mean 28.7 to 33.5 years **Sex:** NR **Defect size:** mean 1.9 to 6 cm^2 **Duration of symptoms:** NR **Other:** 36 to 100% traumatic lesions; 24 to 89% medial femoral condyle, 8.5 to 23% lateral femoral condyle, 0 to 61% patella, 0 to 15.2% trochlea, 0 to 10% lateral tibial condyle / tibial plateau **INTERVENTIONS** ACI: n=5 P-ACI, n=3 C-ACI, n=1 characterised ACI, n=1 Hyalograft C, n=2 MACI; n=3 OAT, n=3 microfracture, n=1 abrasion **OUTCOMES** Clinical outcomes (modified Cincinnati, Stanmore, ICRS, IKDC, KOOS, Lysholm, Meyers, Tegner, VAS), SF-36; histology	
Naveen 2012[46] **Focus:** to determine the effectiveness of ACI when compared with other treatment modalities **Funding:** no specific funding	**INCLUSION CRITERIA** **Study design:** RCTs **Participants:** no criteria specified **Intervention:** ACI versus other treatment modalities (microfracture, mosaicplasty, abrasionplasty, bone marrow–derived mesenchymal stem cell	**Number of included trials:** 17 (but only 13 separate trial populations) **Number of participants:** 1644 (range 21 to 321 per study)(number as stated by authors, only 1339 distinct participants) **TRIALS** **Design:** not specified (n=7	**Inclusion criteria described/adequate:** yes **Literature search described/adequate:** partly; inadequate **Study selection described/adequate:** no **Data extraction**

Review	Inclusion criteria and methodology	Included studies	Quality
	(BMSC), MACI) for cartilage repair in the knee **Outcomes:** clinical outcomes and evaluation scores; histological outcomes **METHODOLOGY** **Search strategy:** *databases:* PubMed, Scopus, NICE, Cochrane CCTR; *date of search:* up to June 2010; only 2 keywords searched; *limitations:* none; *additional searches:* none **Study selection:** as per inclusion criteria, methods not stated (but obviously actual inclusion was different from inclusion criteria) **Quality assessment:** limited, for histological assessments reported blinding of assessors, attrition and level of evidence **Data extraction:** limited, brief note on items extracted but not methodology **Meta-analysis:** no **Data analysis:** text and tables **Subgroup/sensitivity analyses:** ACI versus different comparators	RCTs, n=6 CCT/ comparative cohort) **Follow-up:** 12 months to 5 years **Quality:** classified as level I evidence: n=4, level II: n=8, level III: n=1, level IV: n=2, no classification: n=2 **Origin:** not reported **Funding:** not reported **PARTICIPANTS** **Age:** not reported **Sex:** 57 to 76% male (reported by 14 studies) **Defect size:** mean 1.9 to 6.4 cm^2 **INTERVENTIONS** ACI versus: mosaicplasty n=4, microfracture n=8, MACI n=3, BMSC n=1, abrasionplasty n=1 **OUTCOMES** Clinical scores (subjective outcome, Lysholm, Tegner, Cincinatti, Stanmore, Meyers, IHC, ICRS, IKDC, Hop test, KOOS, Gillquist), quality of life (SF-36), histology / MRI	**described/adequate:** no **Study quality assessment described/adequate:** no **Study flow shown:** yes **Study characteristics of individual studies described:** yes **Quality of individual studies given:** limited **Results of individual studies shown:** yes **Statistical analysis appropriate:** NA **OVERALL QUALITY: low**
Negrin 2013[5] **Focus:** to test the hypothesis that ACI has a better treatment	**INCLUSION CRITERIA** **Study design:** controlled clinical trial or controlled prospective observational study, FU ≥1 year	**Number of included trials:** 6 **Number of participants:** 399 **TRIALS**	**Inclusion criteria described/adequate:** yes **Literature search described/adequate:**

Review	Inclusion criteria and methodology	Included studies	Quality
effect than microfracture and increasing superiority over the years (under similar patient-specific and defect-specific conditions) **Funding:** not reported; the authors state that they have no conflict of interest	**Participants:** patients with full-thickness cartilage defects (Outerbridge grades III and IV) on the medial or lateral femoral condyle, the trochlea, or the patella due to acute or repetitive trauma, osteonecrosis, or osteochondritis dissecans **Intervention:** microfracture (without implantation of a scaffold or injection of substitutes) versus any type of ACI **Outcomes:** clinical scores (functional capacity) **METHODOLOGY** **Search strategy:** *databases:* Medline, Embase; Cinahl, Cochrane CENTRAL; *date of search:* up to March 31 2013; only one search term; *limitations:* none; *additional searches:* none **Study selection:** studies selected by two independent reviewers using standardised forms; discrepancies resolved by consensus **Quality assessment:** for RCTs Cochrane risk of bias tool, for observational studies criteria proposed by Deeks; assessment by two independent reviewers, discrepancies resolved by consensus	**Design:** n=4 RCTs, n=2 comparative cohort **Follow-up:** 1 to 5 (7.5?) years **Quality:** NR **Origin:** NR **Funding:** NR **PARTICIPANTS** **Age:** mean 25.1 to 40.4 years **Sex:** NR **Defect size:** mean 2.0 to 4.8 cm^2 **Duration of symptoms:** NR No other characteristics systematically reported **INTERVENTIONS** n=1 1st generation ACI, n=4 2nd generation ACI, n=1 3rd generation ACI; all versus microfracture **OUTCOMES** Clinical outcome (Lysholm, IKDC, KOOS), treatment failure, histology	yes, but inadequate **Study selection described/adequate:** yes **Data extraction described/adequate:** yes **Study quality assessment described/adequate:** yes **Study flow shown:** yes **Study characteristics of individual studies described:** yes **Quality of individual studies given:** no **Results of individual studies shown:** yes **Statistical analysis appropriate:** no, MAs show substantial heterogeneity which was not explored **OVERALL QUALITY: medium**

Review	Inclusion criteria and methodology	Included studies	Quality
	Data extraction: items extracted are listed **Meta-analysis:** yes **Data analysis:** SMD (random effects model), heterogeneity, funnel plot; text and tables **Subgroup/sensitivity analyses:** duration of FU; generation of ACI		
Vasiliadis 2010[42] **Focus:** to assess the effectiveness and safety of ACI compared to other treatment options (conservative or surgical) for patients who require knee repair of clinically significant, symptomatic defects of the knee joint **Funding:** NR **Note:** refers to a 2010 Cochrane review which is slightly less inclusive (3 of the trials included here were excluded in the Cochrane review (2 were comparisons of different forms of ACI, 1 was excluded because of the heterogeneous patient population))	**INCLUSION CRITERIA** **Study design:** RCTs or quasi-randomised trials **Participants:** 15 to 55 years with symptomatic cartilage defects of the femur or patella (in joints free from rheumatoid arthritis, osteoarthritis) **Intervention:** ACI versus any other intervention **Outcomes:** clinical efficacy and complications **METHODOLOGY** **Search strategy:** *databases:* Cochrane Bone, Joint and Muscle Trauma Group Specialised Register, Cochrane CENTRAL, Medline, Embase, SPORTDiscus, WHO International Trials Registry Platform, Current Controlled Trials; *date of search:* December 2009; reference for search strategy given; *limitations:* none; *additional*	**Number of included trials:** 9 **Number of participants:** 626 (19 to 118 per study) **TRIALS** **Design:** n=8 RCTs, n=1 quasi-RCT **Follow-up:** 10 months to 5 years **Quality:** overall, average to low quality; <75% adequate sequence generation, <50% adequate allocation concealment, <75% incomplete outcome data addressed **Origin:** NR **Funding:** NR **PARTICIPANTS** **Age:** mean 29.7 to 35.4 years **Sex:** 47 to 68% male **Defect size:** mean 1.9 to 6.1 cm^2 **Duration of symptoms:** 1.5 to 10 years **Other:** Location (reported by n=7): medial femoral	**Inclusion criteria described/adequate:** yes **Literature search described/adequate:** yes, but no additional searches mentioned **Study selection described/adequate:** yes **Data extraction described/adequate:** yes **Study quality assessment described/adequate:** yes **Study flow shown:** no **Study characteristics of individual studies described:** yes **Quality of individual studies given:** yes **Results of individual studies shown:** yes **Statistical analysis appropriate:** yes **OVERALL**

Review	Inclusion criteria and methodology	Included studies	Quality
	searches: none **Study selection:** independently by two reviewers, differences resolved by discussion **Quality assessment:** Cochrane risk of bias tool, similarity at baseline; quality assessed by two reviewers independently, differences resolved by discussion **Data extraction:** items extracted reported; authors contacted for missing information; data extracted by two reviewers independently, differences resolved by discussion **Meta-analysis:** no / limited for Cochrane review **Data analysis:** text and tables **Subgroup/sensitivity analyses:** none	condyle 24 to 89%, lateral femoral condyle 5 to 25%, trochlea 0 to 21%, patella 0 to 61%, tibial plateau 0 to 10%, multiple 0 to 13%; Aetiology (n=5): trauma 36 to 92%, osteochondritis dissecans 8 to 28%, chondromalacia patellae 0 to 46%, failed previous surgery 0 to 20%, uncertain 3 to 31% **INTERVENTIONS** ACI n=1, C-ACI n=3, P-ACI n=5, characterised chondrocyte implantation n=1, MACI n=1; microfracture n=2, mosaicplasty n=3, abrasion n=1 **OUTCOMES** Clinical outcomes (Lysholm, Tegner, KOOS, modified Cincinnati, VAS, Mayers, ICRS, Stanmore), SF-36, biopsy, IKDC, complications	**QUALITY: high**
Vavken 2010[53] **Focus:** effectiveness of ACI compared to other treatments with respect to clinical outcome and quality of repair tissue **Funding:** none; authors state that they have no conflict of	**INCLUSION CRITERIA** **Study design:** controlled trials, minimum FU 6 months **Participants:** cartilage defects of the knee **Intervention:** ACI (any type) versus another cartilage repair procedure or placebo **Outcomes:** clinical outcome, quality of repair tissue	**Number of included trials:** 10 (but really only 7 independent trials) **Number of participants:** 441 (range 19 to 118 per study) **TRIALS** **Design:** n=6 RCTs, n=1 quasi-RCT **Follow-up:** 1 to 5 years **Quality:** n=3 level I	**Inclusion criteria described/adequate:** yes **Literature search described/adequate:** yes, although limited search terms **Study selection described/adequate:** partly **Data extraction**

Review	Inclusion criteria and methodology	Included studies	Quality
interest	**METHODOLOGY** **Search strategy:** *databases:* PubMed; Embase, Cochrane CENTRAL, Cinahl, BioMed; *date of search:* December 2009; search strategy shown; *limitations:* none; *additional searches:* bibliographies of relevant papers **Study selection:** records compared against inclusion criteria but no further methodology reported **Quality assessment:** level of evidence determined, quality criteria listed¸ independent assessment by 2 reviewers **Data extraction:** items extracted listed; independent extraction by 2 reviewers **Meta-analysis:** no **Data analysis:** text and tables **Subgroup/sensitivity analyses:** results reported by comparator	evidence, n=4 level II evidence, attrition 0 to 28%, deficits with respect to sample size, randomisation procedure, blinding of outcome assessment **Origin:** NR **Funding:** NR **PARTICIPANTS** **Age:** NR **Sex:** 57 to 68% male **Defect size:** mean 1.9 to 5.1 cm^2 **Duration of symptoms:** NR **Other:** NR **INTERVENTIONS** ACI versus n=3 osteochondral graft transfer, n=3 microfracture, n=1 abrasion **OUTCOMES** Clinical outcome (subjective, Lysholm, Tegner, Meyer, modified Cincinnati, Stanmore, IKDC, KOOS), SF-36, histology, safety	**described/adequate:** yes **Study quality assessment described/adequate:** yes **Study flow shown:** yes **Study characteristics of individual studies described:** yes **Quality of individual studies given:** yes **Results of individual studies shown:** yes **Statistical analysis appropriate:** NA **OVERALL QUALITY: high**

BMSC: bone marrow-derived mesenchymal stem cell; C-ACI: collagen-based ACI; P-ACI: periosteum-based ACI; MACI: matrix-assisted autologous chondrocyte implantation; FU: follow-up; SMD: standardised mean difference

Appendix VII. Results and conclusions of systematic reviews

Table 32. Results and conclusions of systematic reviews

Review	Outcome	N studies	Result of meta-analysis / review	Comments
General ACI vs other				
Mithöfer 2013	Clinical outcome	1 RCT, 5 non-RCTs with ACI, 20 studies overall	Good and excellent results in 82 SE7% (vs 79 SE 5% for all methods) Increase in Tegner activity score was seen in 84 SE6% of patients overall, the highest average Tegner scores were found for ACI; decreasing Tegner scores were seen in 6 studies after initial increase – 5 after microfracture and 1 after OAT, no decrease seen with ACI (36 to 60 months)	
	Return to sports	1 RCT, 5 non-RCTs with ACI, 20 studies overall	Return to sports 33 to 96% with ACI (mean 67 SE17%, versus 73 SE7% for all methods) Time to return to sports 18 SE4 months after ACI (range 12 to 36 months), versus 8 SE1 months after microfracture, 7 SE2 months after osteochondral autograft Return to sports at the pre-injury level 71 SE12% with ACI (versus 68 SE4% overall) Continued sports participation at the pre-injury level (average FU 50 SE7 months) 96 SE4% with ACI versus 52 SE6% with microfracture and 52 SE21% with osteochondral autograft transplantation	

Review	Outcome	N studies	Result of meta-analysis / review	Comments
	Subgroups	1 RCT, 5 non-RCTs with ACI, 20 studies overall	Better results with younger age (<25 to 30 years) Better results with shorter time between diagnosis and surgical treatment (<12 months) Lesion size <2 cm^2 associated with significantly higher return to sports (but no effect of lesion size with ACI) In patients treated with ACI: lower average number of previous surgeries in those who returned to sports; return to sports significantly better and time to return significantly shorter in competitive than recreational athletes	
Vasiliadis 2010	Subgroups	4 RCTs	1 RCT (1 year): no significant difference by anatomical site but none of the patellar lesions had a good arthroscopic result 1 RCT (1 year): patients with previous surgical procedures had worse clinical outcomes, but correlation not statistically significant; longer duration of symptoms before surgery (C-ACI or MACI) significantly correlated to worse clinical outcomes; patients <35 years had significantly better clinical outcomes 1 RCT: onset of symptoms <2 years before surgery associated with larger improvement in KOOS score (microfracture and characterised chondrocyte implantation, <3 years in the latter group) 1 RCT (2 years): patients <30 and more active patients had better results; patients with smaller lesions (<4 cm^2) had better results in the microfracture group only (result independent of lesion size with P-ACI)	

Review	Outcome	N studies	Result of meta-analysis / review	Comments
C-ACI vs P-ACI				
Goyal 2013A	General effectiveness	1 RCT	No statistical difference in results after 2 years	outcomes not specified; actual values not reported for any of the outcomes
	Retreatment	1 RCT 1 cost-effectiveness	Significant number of patients in P-ACI group required periosteal shaving; high risk of patch hypertrophy	
	Cost-effectiveness	1 cost-effectiveness	Both methods cost-effective but C-ACI slightly more so because of risk of hypertrophy with P-ACI	
Harris 2010	Clinical outcome	1 RCT	No significant difference in modified Cincinnati (2 years) and ICRS AKS scores (1 and 2 years)	
	Histology	1 RCT	No significant difference in macroscopic and histologic examination at 1 and 2 years but 36% in the P-ACI group versus 0% in the C-ACI group needed arthroscopic knee surgery because of hypertrophy at 1 year	
Nakamura 2009	Clinical outcome	1 RCT	No significant difference in modified Cincinnati and ICRS AKS scores (2 years)	
	Histology	1 RCT	Significant number of patients in P-ACI group required shaving of hypertrophied graft	
Vasiliadis 2010	Clinical outcome	1 RCT	No significant difference in modified Cincinnati score at 2 years (good and excellent results in 66.7% with C-ACI and 74.3% with P-ACI)	
	Histology	1 RCT	81% good to excellent results with P-ACI and 79% with C-ACI according to ICRS evaluation system (1 year, p=NS), but biopsies better for C-ACI (statistical significance unclear)	

Review	Outcome	N studies	Result of meta-analysis / review	Comments
	Complications	1 RCT	12/31 (1 year) and 1/9 (2 years) graft hypertrophies with P-ACI, 1/35 (2 years) with C-ACI	
General MACI and 2nd generation ACI				
Kon 2009	Clinical outcome	18 studies (incl. 2 RCTs, 3 additional comparative studies)	Mean subjective preoperative IKDC score ranged from 37.0 to 41.1 and improved to 70.2 to 80.2 at 5 years (results at earlier time points 73.6 to 80.6) Mean preoperative Lysholm score ranged from 46.3 to 57.5 and improved to 80.8 at 3 years (results at earlier time points 69.7 to 96.7)	
	Complications	8 studies	n=7 graft hypertrophy (4 for MACI, 2 for Hyalograft C, 1 for BioSeed), n=4 joint stiffness (3 for MACI and 1 for Hyalograft C), n=1 graft detachment for MACI, n=1 synovitis for Hyalograft C) One study reported n=3 hypertrophy, n=3 graft detachments, and n=1 partial ossification with atelocollagen scaffold (only product used in conjunction with a periosteal flap; impossible to determine if the complication was related to the periosteal flap)	
ACI vs MACI				
Naveen 2012	Clinical outcome	1 RCT, 2 comparative cohort	1 RCT and 1 comparative cohort no significant difference in clinical outcomes (2 years), 1 comparative cohort significantly better clinical outcomes for MACI, higher complication rate with ACI (4.5 years)	actual values not reported for any of the outcomes

Review	Outcome	N studies	Result of meta-analysis / review	Comments
C-ACI vs MACI				
Goyal 2013A	Knee function / clinical scores	1 RCT	Improvements in all clinical scores with both techniques after 1 year	actual values not reported for any of the outcomes
	Arthroscopic / histologic assessment	1 RCT	No significant difference after 1 year	
Magnussen 2008	Clinical outcome	1 RCT	No significant difference between groups in modified Cincinnati, VAS and Stanmore scores (1 year)	
	Arthroscopic / histologic assessment	1 RCT	International Cartilage Repair Society cartilage repair assessment (CRA, 12=normal cartilage); CRA 8-12, no significant difference (C-ACI 79.2%, MACI 66.6%) (1 year) Percent with hyalinelike or mixed hyaline/fibrocartilage, no significant difference (C-ACI 42.9%, MACI 36.4%) (1 year)	
	Subgroups	1 RCT	Patients <35 years had better clinical outcome (p=0.03)	
	Complications	1 RCT	C-ACI: 6.8% arthofibrosis, 9.1% tissue hypertrophy MACI: 6.4% arthofibrosis, 6.4% tissue hypertrophy, 2.1% superficial wound infection	
Nakamura 2009	Clinical outcome	1 RCT	No significant difference between groups in modified Cincinnati, VAS, ICRS AKS and Stanmore scores (2 years)	
Vasiliadis 2010	Clinical outcome	1 RCT	No significant difference in modified Cincinnati score (outcome good or excellent in 59.1% after C-ACI, in 72.3% after MACI, 12 months), no significant difference in VAS or Stanmore score	

Review	Outcome	N studies	Result of meta-analysis / review	Comments
	Histology	1 RCT	79.2% good to excellent results with C-ACI and 66.6% with MACI according to ICRS evaluation system (1 year, p=NS), with hylinelike or mixed hyalinelike repair tissue in 42.9% with C-ACI and 36.4% with MACI	
P-ACI vs MACI				
Goyal 2013A	Knee function	1 RCT	At 2 years, no significant difference between groups in IKDC scores and Tegner activity scores between groups; Lysholm and Gillquist scores (function) favoured P-ACI group	actual values not reported for most of the outcomes
	Quality of life	1 RCT	At 2 years, no significant difference between groups in SF36 scores	
	MRI cartilage repair tissue score	1 RCT	At 1 and 2 years, no significant difference	
Harris 2010	Clinical outcome	2 RCTs	No significant difference in clinical scores after 1 year (IKDC, Lysholm, Tegner, ICRS, modified Cincinnati)	
Open vs arthroscopic ACI				
Harris 2010	Clinical outcome	1 comparative cohort	IKDC (objective) results significantly better for arthroscopic group at 1 year (effect size 0.58 SE0.21) but no significant difference at 5 years	
ACI vs mosaicplasty / osteochondral autograft transfer				

Review	Outcome	N studies	Result of meta-analysis / review	Comments
Bekkers 2009	Clinical outcome	1 RCT	No significant difference in modified Cincinnati good-excellent score (>55) at 19 months (ACI 88%, mosaicplasty 69%) Significant difference in modified Cincinnati good-excellent score (>55) at 12 months for medial femur (ACI 88%, mosaicplasty 73%, p=0.032) but not lateral femur or patella	
	Macroscopic / histologic outcome	1 RCT	ICRS macroscopic grading significantly better with ACI at 12 months (excellent-good ACI 82%, mosaicplasty 34%, p<0.01) Only biopsies from ACI group (n=7 predominantly hyaline, n=7 mixed hyaline and fibrocartilage, n=5 predominantly fibrocartilage)	
Harris 2010	Clinical outcome	1 RCT, 1 CCT	1 RCT no significant difference in Lysholm score after 1 year 1 CCT Lysholm score significantly better after 1 year for mosaicplasty but no significant difference at 2 years	
Magnussen 2008	Clinical outcome	1 RCT, 1 CCT	1 RCT no significant difference in modified Cincinnati >55 (ACI 88%, OAT 69%, p=0.27)(1 year) 1 CCT significantly better Lysholm scores with OAT (P-ACI 67 SD8, OAT 74 SD6, p<0.05), no significant difference in Tegner or Meyers scores (2 years)	

Review	Outcome	N studies	Result of meta-analysis / review	Comments
	Arthroscopic / histologic assessment	1 RCT, 1 CCT	1 RCT percent with CRA 8 to 12 significantly better with ACI (ACI 82%, OAT 34%, p<0.01); 74% of ACI patients with hyalinelike or mixed hyaline / fibrocartilagelike (not reported for OAT)(1 year) 1 CCT OAT patients with hyaline cartilage not integrated into surrounding cartilage; P-ACI specimens with mainly fibrocartilage, focalised areas or hyalinelike cartilage (2 years)	
	Subgroups	1 RCT, 1 CCT	1 RCT significantly more with modified Cincinnati >55 with ACI of patients with femoral condyle lesions only (ACI 88%, OAT 74%, p=0.03)(1 year)	
	Complications	1 RCT, 1 CCT	1 RCT 7 poor results, all in OAT group (1 year) Arthofibrosis ACI 0 to 15%, OAT 7.1 to 15% (up to 2 years) OAT group only: Superficial wound infection 2.4 to 5%, deep vein thrombosis 2.4%, postoperative haemarthrosis (10%)	
Nakamura 2009	Clinical outcome	2 RCTs, 1 CCT	1 RCT modified Cincinnati significantly better for ACI than OAT in the medial femoral condyle (19 months) 1 RCT no significant difference in Lysholm scores, IKDC (36 months); 1 CCT significantly better Lysholm scores with OAT (2 years)	

Review	Outcome	N studies	Result of meta-analysis / review	Comments
Naveen 2012	Clinical outcome	2 RCTs, 1 CCT	1 CCT no difference in clinical scores, improvement with ACI lagged behind improvement with mosaicplasty (2 years) 1 RCT 88% good and excellent after ACT, 69% after mosaicplasty ($p<0.05$, 19 months) 1 RCT complete recovery in 68% after ACI, 88% after mosaicplasty (but difference presumably non-significant as treatments are considered equivalent, 36 months)	actual values not reported for any of the outcomes
	Histological outcome	1 RCT, 1 CCT	1 CCT: fibrocartilaginous defect filling with ACI, no visible changes in tissue after mosaicplasty (24 months) 1 RCT: 82% good or excellent after ACI, 34% after mosaicplasty (19 months)	
Vasiliadis 2010	Clinical outcome	2 RCTs, 1 CCT	1 CCT: significantly better recovery (Lysholm) with mosaicplasty than P-ACI (up to 2 years, $p=0.012$), no significant difference in Tegner or Meyers score 1 RCT: no significant difference in Lysholm score (10 months) 1 RCT: no significant overall difference between P-ACI / C-ACI and mosaicplasty, but ACI significantly better for medial femoral condyle lesions at 12 months (88% good or excellent results vs 74% for mosaicplasty, $p=0.032$)	
(Cochrane review)	Satisfactory outcome	2 RCTs, 1 CCT	MA showed no significant difference (risk ratio 1.02, 95% CI: 0.81, 1.28, p=NS), significant heterogeneity	

Review	Outcome	N studies	Result of meta-analysis / review	Comments
	Histology	2 RCTs	1 RCT: 82% good or excellent after ACI, 34% after mosaicplasty (12 months, $p<0.01$) – fibrous tissue between grafts in 4 mosaicplasty patients, plugs disintegrated in 3, in 1 ACI patients with mixed hyaline-fibrohyaline repair tissue ongoing maturation of repair tissue to hyaline-like tissue was seen 2 years postoperatively 1 RCT: only short term results – fibrocartilage in central and superficial layers and hyaline cartilage only in deep-layer areas 6 months after ACI, good quality of cartilage of transplanted plugs (but >50% of biopsies taken at 3 months)	
	Complications	1 CCT	No significant differences in complication rates	
Vavken 2010	Clinical outcome	2 RCTs, 1 CCT	1 RCT no significant difference 1 RCT complete recovery in 68% after ACI, 88% after mosaicplasty 1 RCT 88% good and excellent after ACT, 69% after mosaicplasty ($p<0.05$, 19 months)	
	Histology	2 RCTs	1 RCT fibrocartilagenous filling after ACI, no visible changes in tissue after OAT (2 years) 1 RCT: 82% good or excellent after ACI, 34% after mosaicplasty (19 months)	
	Complications	1 RCT, 1 CCT	1 RCT: 4 failed treatments with OAT 1 CCT: gaps between plugs and adjacent tissue in all second look arthroscopies	

Review	Outcome	N studies	Result of meta-analysis / review	Comments
ACI vs microfracture				
Bekkers 2009	Clinical outcome	2 RCTs	1 RCT characterised chondrocyte implantation versus microfracture no significant difference in KOOS score at 18 months 1 RCT ACI versus microfracture no significant difference in Lysholm, VAS or Tegner scores at 5 years; SF-36 physical functioning significantly better with microfracture at 2 years (p=0.01), no significant difference at 5 years	
	Macroscopic / histologic outcome	2 RCTs	1 RCT significantly higher histomorphometric score with characterised chondrocyte implantation than with microfracture (p=0.003) as well as significantly higher histology assessment score (p=0.012) 1 RCT no significant difference in ICRS macroscopic grading between ACI and microfracture at 2 years; histology (n=67): hyaline ACI 19%, MF 11%; hyaline/fibrocartilage ACI 31%, MF 17%; fibrocartilage ACI 34%, MF 57%; no tissue ACI 16%, MF 15%	
	Subgroups	1 RCT	Better clinical outcomes for both groups for age <30 years (p=0.007 at 2 years and p=0.013 at 5 years) Lesions <4 cm^2 showed better clinical results in the microfracture group (p<0.003)	
Goyal 2013B	Clinical outcome	7 comparative	Numerical data only reported for microfracture, no results reported for comparison with ACI	

Review	Outcome	N studies	Result of meta-analysis / review	Comments
Harris 2010	Clinical outcome	6 RCTs, 1 CCT	Participants in 3/7 studies had significantly better clinical scores after 1 to 5 years with ACI than with microfracture (effect sizes for Lysholm, Tegner, ICRS, KOOS scores 0.66 to 1.52); no significant difference for the rest of the studies (KOOS, Lysholm, SF-36 physical component); 1 RCT hat significantly better results on the SF-36 physical component at 2 years for microfracture (effect size -0.65 for ACI)	
	Histological outcome	1 RCT	1 RCT had a significant difference in histomorphologic and histology score in favour of ACI at 1 year	
	Durability	2 RCTs, 1 CCT	Clinical results for microfracture tended to plateau or deteriorate at longer follow-ups, while results for ACI tended to improve (3 studies); at 5 years, sports activity remained stable in the ACI group but declined in the microfracture group (1 CCT)	
Magnussen 2008	Clinical outcome	1 RCT	At 2 years, no significant difference in Lysholm or VAS scores (2 years) SF-36 physical component significantly better with microfracture (46 SD2 vs P-ACI 42 SD2, p=0.01)	
	Arthroscopic / histologic assessment	1 RCT	At 2 years, no significant difference in CRA No significant difference in percentage with hyalinelike or mixed hyaline / fibrocartilagelike (microfracture 29%, P-ACI 50%, p=0.08)	

Review	Outcome	N studies	Result of meta-analysis / review	Comments
	Subgroups	1 RCT	At 2 years, patients <30 years (p=0.007) and patients with Tegner scores >4 (p=0.0005) had better SF-36 scores in both groups; higher SF-36 scores in microfracture group associated with lesions <4 cm^2 (p=0.003)	
	Complications	1 RCT	P-ACI: 25% tissue hypertrophy Microfracture: 7.5% tissue hypertrophy, 2.5% arthofibrosis	
Mithöfer 2013	Clinical outcome	1 RCT	higher increases in KOOS sports and recreation with ACI than microfracture	
	Histology	1 RCT	Significantly better histological assessment (p<0.05) and histomorphometric scores, including higher proteoglycan content, higher type II collagen content, and more normal chondrocyte morphology (p<0.01) after characterised ACI compared with microfracture at 12-18 months	
Nakamura 2009	Clinical outcome	2 RCTs, 1 CCT	1 RCT, no significant difference in Lysholm, Tegner, VAS scores; SF-36 physical component significantly better with microfracture (2 years); no significant difference in any of the scores at 5 years 1 RCTs no significant difference in KOOS scores (18 months) 1 CCT significantly better IKDC scores with ACI at 5 years	
	Histology	2 RCTs	No significant difference in 1 RCT (2 years), better result for ACI in 1 RCT (18 months)	

Review	Outcome	N studies	Result of meta-analysis / review	Comments
Naveen 2012	Clinical outcome	3 RCTs, 2 comparative cohort	No significant difference in clinical scores in 1 RCT and 1 comparative cohort (2 to 5 years), ACI better in 1 RCT and 1 comparative cohort (12 months to 5 years), 1 RCT no significant difference at 18 months but ACI significantly better at 36 months	actual values not reported for any of the outcomes
	Histological outcome	2 RCTs	No significant difference in 1 RCT (2 years), better result for ACI in 1 RCT (18 months)	
	Quality of life (SF-36)	2 RCTs	No significant difference in 1 RCT (5 years), better result for microfracture in 1 RCT (2 years)	
Negrin 2013	Clinical outcome	4 RCTs	At 1 year, SMD 1.05 (95% CI: -1.35, 3.45), p=NS; heterogeneity p<0.0001	
		4 RCTs, 1 comparative cohort	At 2 years, SMD 0.38 (95% CI: -0.13, 0.90), p=NS; heterogeneity p=0.0008	
		2 RCTs, 1 comparative cohort	At 5 years, SMD 0.28 (95% CI: -0.23, 0.79), p=NS; heterogeneity p=0.0143	
	Subgroups – 2nd and 3rd generation ACI	3 RCTs	At 1 year, SMD 2.22 (95% CI: 1.01, 3.42), p<0.05; heterogeneity p=0.0003	
		3 RCTs, 1 comparative cohort	At 2 years, SMD 0.56 (95% CI: 0.30, 0.82), p<0.05; heterogeneity p=NS	
		1 RCT, 1 comparative cohort	At 5 years, SMD 0.51 (95% CI: 0.21, 0.80), p<0.05; heterogeneity p=NS	
	Treatment failure	4 RCTs, 2 comparative cohort	Overall, 21 treatment failures with microfracture versus 16 with ACI	

Review	Outcome	N studies	Result of meta-analysis / review	Comments
	Histology	2 RCTs	1 RCT no significant difference between ACI and microfracture, but ACI biopsy specimens tended to have a more hyalinelike appearance 2 years postoperatively 1 RCT clear morphological superiority of cartilaginous tissue after ACI; microfracture resulted in significantly lower histological scores for type II collagen and matrix proteoglycan content	
Vasiliadis 2010	Clinical outcome	3 RCTs	1 RCT: no significant difference between P-ACI and microfracture (5 years) in Lysholm or Tegner scores or VAS, SF-36 significantly better with microfracture at 2 years but no significant difference at 5 years 1 RCT: MACI more improvement in Lysholm and Tegner scores than microfracture but unclear if the difference was significant (12 months) 1 RCT: no significant difference in modified KOOS score at 18 months, characterised chondrocyte implantation slightly better at 36 months (p=0.05), slower recovery with characterised chondrocyte implantation, but no significant difference in function at 2 years	

Review	Outcome	N studies	Result of meta-analysis / review	Comments
	Histology	2 RCTs	1 RCT (12 months) significantly better histomorphogenic score(p=0.003) and better mean histology score (p=0.012) with characterised chondrocyte implantation than microfracture – obvious cartilaginous restoration after chondrocyte implantation, repair scar tissue after microfracture 1 RCT 71.4% poor quality repair tissue with microfracture vs 50% with P-ACI (2 years) but no statistically significant difference, no association between histological quality and clinical outcomes at 2 and 5 years, but the worse the image at 2 years, the bigger the risk of failure up to 5 years (p=0.02)	
	Complications	2 RCTs	1 RCT (2 years): 25% debridement due to graft hypertrophy with P-ACI, 10% with microfracture, 23% in each group had a failure (1 in each group a total arthroplasty) 1 RCT (3 years): similar complication rates with characterised chondrocyte implantation and microfracture, 2/57 failures with characterised chondrocyte implantation and 7/61 with microfracture	
Vavken 2010	Clinical outcome	3 RCTs	1 RCT (12 months) significantly better results with ACI than microfracture, 1 RCT no significant difference in clinical scores (2 and 5 years), 1 RCT no significant difference at 18 months but ACI significantly better at 36 months; 1 RCT SF-36 significantly better with microfracture than ACI at 2 years but not at 5 years	

Review	Outcome	N studies	Result of meta-analysis / review	Comments
	Histology	2 RCTs	1 RCT no significant difference (2 years), 1 RCT better results for ACI at 18 months	
	Complications	2 RCTs	1 RCT: 9 failures in each group, 25% debridement with ACI and 10% with microfracture (after 5 years) 1 RCT: 25% cartilage hypertrophy with ACI, 13% with microfracture, 67% and 59% adverse events with ACI and microfracture (9% and 13% serious)	
ACI vs BMSC				
Naveen 2012	Clinical outcome	1 comparative cohort	Significantly better clinical outcomes for BMSC than ACI (2 years)	actual values not reported for any of the outcomes
	Histological outcome	1 comparative cohort	Comparison not possible: histological results only presented for BMSC, not ACI	
ACI vs abrasionplasty				
Naveen 2012	Clinical outcome	1 RCT	Significantly better clinical outcomes for ACI (12 months)	actual values not reported for any of the outcomes
Magnussen 2008	Clinical outcome	1 RCT	At 1 year, significantly better clinical scores in MACI than abrasion group (Lysholm MACI 86 SD9, abrasion 74 SD11 ($p=0.001$); IKDC MACI 76 SD13, abrasion 68 SD10 ($p<0.05$); Tegner MACI 5.9 SD0.8, abrasion 4.2 SD.1 ($p<0.01$))	
	Histological outcome	1 RCT	At 1 year, histology on 4 samples (presumably MACI): evidence of hyalinelike cartilage; fibroblastlike cells in two	
	Complications	1 RCT	24% reactive synovitis in MACI group	

Review	Outcome	N studies	Result of meta-analysis / review	Comments
Nakamura 2009	Clinical outcome	1 RCT	At 1 year, significantly better Lysholm and IKDC scores with MACI than abrasion	
Vasiliadis 2010	Clinical outcome – Lysholm scores	1 RCT	ACI significantly better than abrasion at 1 year ($p<0.001$ for improvement in Lysholm scores, 72% with ACI vs 40% with abrasion good or excellent results; $p<0.01$ for difference in Tegner score), IKDC subjective score also significantly better for ACI	
Vavken 2010	Clinical outcome	1 RCT	Significantly better clinical outcomes for ACI (12 months)	

ACI: autologous chondrocyte implantation; AKS: arthroscopic knee surgery; C-ACI: collagen-based ACI; CRA: International Cartilage Repair Society cartilage repair

Table 33. Systematic review conclusions

Study	Conclusions	Recommendations	Comments
Bekkers 2009	**Clinical outcomes:** All trials showed an improvement from clinical baseline scores, regardless of treatment; lesion size, activity level, and patient age are factors that should be considered in selecting treatment of articular cartilage lesions of the knee	**Practice:** small chondral and osteochondral lesions (<1 cm^2) should preferably be treated by microfracture or single-plug OAT; for larger lesions (>4 cm^2) microfracture has been associated with limited effectiveness; for larger lesions, OAT and ACI are both good treatment options **Research:** patients in trials should be stratified based on body mass index, defect location, and post-debridement defect size; outcomes should be reported after at least 2 years of follow-up using biopsy, MRI, and validated clinical outcome tools, including assessment of activity level	

Study	Conclusions	Recommendations	Comments
Goyal 2013A	**General:** C-ACI is marginally more effective than P-ACI, with evidence limited to a follow-up period of 2 years; MACI gives comparable results to P-ACI or C-ACI (evidence from studies with a short duration of follow-up with a small sample size and medium-sized defects in a younger age group)	**Practice:** not reported **Research:** multi-centre RCTs with adequate sample size needed of second and third generation ACI versus first generation ACI; cohort studies of long term effects (10 years) needed	
Goyal 2013B	Only refers to microfracture		Publications including the same study populations counted as separate studies

Study	Conclusions	Recommendations	Comments
Harris 2010	**General:** studies were very heterogeneous and had important quality limitations **Clinical outcomes:** Intermediate-term clinical outcomes after ACI tended to be better than after microfracture; difference compared to osteochondral autograft unclear; no significant differences in clinical outcomes between first and second generation ACI **Histology:** ACI may provide a more durable repair tissue than microfracture **Modifying factors:** outcomes tended to be better for younger patients (<30/35 years), more active patients, patients with shorter symptom duration, and patients who had not had a previous failed surgical intervention; possibly better results for smaller lesions and better effects of ACI than other techniques for larger lesions **Complications:** Graft hypertrophy highest with ACI-P (22%), lower with other methods (4 to 7%); reported 'failure' rates slightly lower with ACI (2.8%) than with microfracture (3.7%) or mosaicplasty (7.1%)	**Practice:** ACI may be the best option for large defects in young, active patients with a short duration of symptoms and no previous cartilage surgery; microfracture is indicated for smaller defects in young, active patients; osteochondral autograft may provide a more rapid improvement in terms of clinical outcome but is limited by donor site morbidity **Research:** higher quality studies needed, with the following characteristics: proper and transparent patient enrolment with clearly stated inclusion and exclusion criteria; proper independently performed randomisation techniques; no concurrent surgical interventions (anterior cruciate ligament reconstruction, realignment osteotomy, meniscal surgery, etc.); consistent surgical technique; longer clinical follow-up with an independent observer; use of validated, responsive, and reliable outcome measures; clear reporting of data with a statement of both clinical relevance and significance	Publications including the same study populations counted as separate studies

Study	Conclusions	Recommendations	Comments
Kon 2009	**Clinical outcomes:** matrix-assisted second generation ACI is a promising technique for the treatment of isolated chondral defects; good clinical results were reported by all products, but follow-ups were short and quality levels of studies low	**Practice:** not reported **Research:** high quality long term RCTs are needed	
Magnussen 2008	**General:** follow-up relatively short, heterogeneous outcome measures **Clinical outcomes:** all trials revealed short-term improvement in all clinical scores with every treatment method evaluated (ACI, MACI, OAT, microfracture, abrasion)	**Practice:** microfracture ideal first line treatment for small stage III or IV articular cartilage defects; more complex surgery needed for larger lesions (larger than 2 to 4 cm^2) **Research:** large multicentre trial needed comparing ACI, MACI, OAT, microfracture, simple débridement, and a nonoperative control; trial should use validated patient-oriented clinical outcome measures, e.g. the Knee Injury and Osteoarthritis Outcome Score, the WOMAC Osteoarthritis Index, SF-36 score, or the International Knee Documentation Committee score, with FU at 5 and 10 years	

Study	Conclusions	Recommendations	Comments
Mithöfer 2009	**Return to sports:** return to sports was possible in 73% overall, with highest return rates after osteochondral autograft transplantation; time to return to sports was between 7 and 18 months (longest with ACI); initial return to sports at the pre-injury level was possible in 68% and did not significantly vary between surgical techniques; continued sports participation at the pre-injury level was possible in 65%, with the best durability after ACI; several factors affected the ability to return to sport after ACI: athlete's age (better at younger age), preoperative duration of symptoms (better with shorter duration)	**Practice:** not reported **Research:** systematic research is needed to explain lack of return to sports and unsustained sports participation in some patients; prospective long term studies are needed to determine if articular cartilage repair in athletes can influence the high incidence of osteoarthritis associated with high impact sports	
Nakamura 2009	**General:** studies were of limited quality; there is insufficient evidence from the included studies to say whether cell-based therapy is superior to other treatment strategies in articular cartilage lesions of the knee	**Practice:** not reported **Research:** high quality RCTs with long term follow-up are needed	Publications including the same study populations counted as separate studies

Study	Conclusions	Recommendations	Comments
Naveen 2012	**Clinical outcomes:** there is heterogeneity and inconsistency between studies; it is unclear to what extent any differences between treatments in clinical outcomes are clinically important **Histology:** ACI is associated with superior structural regeneration of cartilage tissue compared to other methods (but only reported by 6/17 studies)	**Practice:** not reported **Research:** studies of long term effects needed	Stated that non-RCTs were excluded but not all of the included trials were RCTs; publications including the same study populations counted as separate studies
Negrin 2013	**Clinical outcomes:** the meta-analyses (of all forms of ACI versus microfracture or only 2nd and 3rd generation ACI) did not reveal any clinically relevant superiority of ACI over microfracture, results converged over time; decision making must take patient objectives, physical demands, and patient- and defect-specific factors into consideration (e.g. microfracture has worse outcomes with defect sizes >4 cm^2)	**Practice:** not reported **Research:** large, well-designed, long term multicentre studies needed	

Study	Conclusions	Recommendations	Comments
Vasiliadis 2010	**General:** studies are of poor quality, heterogeneity regarding techniques followed and populations studied **Clinical outcomes:** body of evidence does not suggest superiority of ACI over other techniques; complication rates were comparable between interventions except from an increased rate of graft hypertrophies after P-ACI; ACI is an effective treatment for full thickness chondral defects of the knee, providing an improvement of clinical outcomes	**Practice:** there is insufficient evidence to conclude whether autologous cartilage implantation is superior to other treatment strategies for treating full thickness articular cartilage defects in the knee. **Research:** need for more high quality RCTs and for uniformity of their reported outcomes; more studies should be done on maturation process of finally formed repair tissue and appropriate rehabilitation programmes for the different techniques; more information and research is needed to compare chondrocyte techniques with conservative treatment such as intensive physiotherapy; further information is needed on the relationship between clinical, histological and radiological outcomes, and the most appropriate measure of functional outcomes that relate to a generic measure of health-related quality of life	

Study	Conclusions	Recommendations	Comments
Vavken 2010	**General:** rather low overall quality of studies, incl. high attrition rates and small sample sizes **Clinical outcomes:** some evidence for better clinical outcomes with ACI compared to OAT and equivalent outcomes with microfracture in studies with higher validity; higher quality repair tissue with ACI compared to other procedures; unclear if statistical significance corresponds to real clinical significance	**Practice:** no clear recommendation regarding ACI versus other treatments possible **Research:** evolution of techniques needs to be taken into account; further high quality studies needed	

Appendix VIII. Economic search strategies

Medline search strategy (1946 to July 2014)

1. exp Economics/
2. exp "Costs and Cost Analysis"/
3. exp Cost-Benefit Analysis/
4. Health Status/
5. exp "Quality of Life"/
6. exp Quality-Adjusted Life Years/
7. (pharmacoeconomic* or pharmaco-economic* or economic* or cost*).tw.
8. (health state* or health status).tw.
9. (qaly* or ICER* or utilit* or EQ5D or EQ-5D or euroqol or euro-qol or short-form 36 or short form 36 or SF-36 or SF36 or SF-6D or SF6D or SF-12 or SF12 or health utilities index or HUI).tw.
10. (markov or time trade off or TTO or standard gamble or SG or hrql or hrqol or disabilit* or disutilit* or net benefit or net-benefit or contingent valuation).tw.
11. (quality adj2 life).tw.
12. (decision adj2 model).tw.
13. (quality of wellbeing or qwb visual analog* scale* or discrete choice experiment* or health* year* equivalen* or hyes or hye or 15-D or 15D or (willing* adj2 pay)).tw.
14. ("resource use" or resource utili?ation or resource$).tw.
15. (utility* adj2 (value* or index* or health or measure* or estimate*)).tw.
16. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. exp Chondrocytes/tr [Transplantation]
18. exp Cartilage, Articular/tr [Transplantation]
19. exp Transplantation, Autologous/
20. (MACI or MACT or chondrocelect or ACI).tw.
21. (chondrocyte* adj4 (implant* or transplant* or matrix or characteri*)).tw.
22. (autologous adj3 (implant* or transplant* or chondrocyte* or cartilage)).tw.
23. (cartilage* adj2 (transplant* or implant*)).tw.
24. 17 or 18 or 19 or 20 or 21 or 22 or 23
25. Knee/ or knee*.mp.
26. 24 and 25
27. Animals/
28. Humans/
29. 27 not 28

30. 26 not 29
31. 16 and 30
32. limit 31 to yr="2004 -Current"

Embase search strategy (1947 to July 2014)

1. exp health economics/
2. exp health status/
3. exp "quality of life"/
4. exp quality adjusted life year/
5. (pharmacoeconomic* or pharmaco-economic* or economic* or cost*).tw.
6. (health state* or health status).tw.
7. (qaly* or ICER* or utilit* or EQ5D or EQ-5D or euroqol or euro-qol or short-form 36 or SF-36 or SF36 or SF-12 or SF12 or SF36 or SF-6D or SF6D or health utilities index or HUI).tw.
8. (markov or time trade off or TTO or standard gamble or SG or hrql or hrqol or disabilit* or disutilit* or net benefit* or contingent valuation).tw.
9. (quality adj2 life).tw.
10. (decision adj2 model).tw.
11. ("quality of wellbeing" or "quality of well-being" or qwb or visual analog* scale* or discrete choice experiment* or health* year* equivalen* or hye* or (willing* adj2 pay)).tw.
12. resource*.tw.
13. (utility* adj2 (value* or index* or health or measure* or estimate*)).tw.
14. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. exp *chondrocyte implantation/
16. (MACI or MACT or chondrocelect or ACI).tw.
17. (chondrocyte* adj4 (implant* or transplant* or matrix or characteri*)).tw.
18. (autologous adj3 (implant* or transplant* or chondrocyte* or cartilage)).tw.
19. (cartilage* adj2 (transplant* or implant*)).tw.
20. 15 or 16 or 17 or 18 or 19
21. exp knee/
22. knee*.tw.
23. 21 or 22
24. 20 and 23
25. (rat or rats or pig or pigs or porcine or mice or murine or mouse or sheep or rabbit* or canine or dog*).ti.
26. 24 not 25
27. 14 and 26
28. limit 27 to yr="2004 -Current"

Search strategy for Web of Science Core Collection (2004 to July 2014)

TOPIC: (cost* or economic* or qaly* or "quality of life" or E ...More TOPIC: (cost* or economic* or qaly* or "quality of life" or EQ-5D or ICER* or utlit* or health stat* or resource* or SF-36 or short form* or markov or standard gamble or time trade) AND TITLE: (autologous chondrocyte or autologous cartilage or MACI or MACT or chondrocelect) AND TOPIC: (knee*)

Search strategy for NHS Economic Evaluation Database: Issue 2 of 4, April 2014

Search on '(autologous chondrocyte or autologous cartilage or MACI or MACT or chondrocelect) and knee* in Title, Abstract, Keywords in Economic Evaluations'

Appendix IX. Critical appraisal of the economic evaluation studies using the CHEERS checklist

B1. Critical appraisal of the economic evaluation studies using the CHEERS checklist

CHEERS checklist (Husereau et al, 2013)	Derrett et al (2005)	Gerlier et al (2010)	Samuelson et al (2012)	Koerber et al (2013)
Title and abstract				
1 Title: Identify the study as an economic evaluation, or use more specific terms such as ``cost-effectiveness analysis``, and describe the interventions compared.	Y*	Y	Y	N
2 Abstract: Provide a structured summary of objectives, methods including study design and inputs, results including base case and uncertainty analyses, and conclusions.	Y	Y	Y	N
Introduction				
3 Background & objectives: Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	Y	Y	Y	N
Methods				
4 Target Population and Subgroups: Describe characteristics of the base case population and subgroups analysed including why they were chosen.	Y	Y*	Y*	Y
5 Setting and Location: State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Y	Y*	Y*	Y*
6 Study perspective: Describe the perspective of the study and relate this to the costs being evaluated.	N	Y	N	Y
7 Comparators: Describe the interventions or strategies being compared and state why they were chosen.	Y	Y	Y*	Y
8 Time Horizon: State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Y	Y	Y	Y
9 Discount Rate: Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	N	Y	Y	Y
10 Choice of Health Outcomes: Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Y	Y	Y*	Y
11a Measurement of Effectiveness - Single Study-Based Estimates: Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	Y	N/A	N/A	N/A
11b Measurement of Effectiveness - Synthesis-based Estimates: Describe fully the methods used for identification of included studies and clinical effectiveness data synthesis of clinical effectiveness data.	N/A	Y	Y	Y*
12 Measurement and Valuation of Preference-based Outcomes: If applicable, describe the population and methods used to elicit preferences for health	Y	Y	Y	Y*

outcomes.				
13a Estimating Resources and Costs - Single Study-based Economic evaluation: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Y	N/A	N/A	N/A
13b Estimating Resources and Costs - Model-based Economic Evaluation: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	N/A	Y	Y	Y*
14 Currency, Price Date and Conversion: Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Y	Y	Y*	Y*
15 Choice of Model: Describe and give reasons for the specific type of decision-analytic model used. Providing a figure to show model structure is strongly recommended.	N/A	Y	Y*	Y*
16 Assumptions: Describe all structural or other assumptions underpinning the decision-analytic model.	N/A	Y	Y*	Y*
17 Analytic Methods: Describe all analytic methods supporting the evaluation. This could include methods for dealing with skewed, missing or censored data, extrapolation methods, methods for pooling data, approaches to validate a model, and methods for handling population heterogeneity and uncertainty.	Y	Y*	N	N
Results				
18 Study parameters: Report the values, ranges, references, and if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. We strongly recommend the use of a table to show the input values.	Y	Y*	Y*	Y
19. Incremental costs and outcomes: For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Y	Y	N	Y
20a Characterizing Uncertainty - Single study-based economic evaluation: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness, parameters together with the impact of methodological assumptions.	Y*	N/A	N/A	N/A
20b Characterizing Uncertainty - Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and	N/A	Y	Y	Y*

assumptions.				
21 Characterizing Heterogeneity: If applicable, report differences in costs, outcomes or in cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	N	N	N	N
Discussion				
22 Study Findings, Limitations, Generalizability, and Current Knowledge: Summarize key study findings and describe how they support the conclusions reached. Discuss limitations and the generalizability of the findings and how the findings fit with current knowledge.	Y	Y	Y*	Y
Other				
23 Source of Funding: Describe how the study was funded and the role of the funder in the identification, design, conduct and reporting of the analysis. Describe other non-monetary sources of support.	Y	Y	Y	Y
24 Conflicts of Interest: Describe any potential for conflict of interest among study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors' recommendations	N	N	Y	Y

Key: Y = yes, No = no, N/A = not applicable and * = partially completed

Appendix B2: Critical appraisal of the economic models using an adapted Phillips checklist

	Philips et al (2006)	Gerlier et al (2010)	Samuelson et al (2012)	Koerber et al (2013)
STRUCTURE				
1	Is there a clear statement of the decision problem?	Y	Y	N
2	Is the objective of the model evaluation and model specified and consistent with the stated decision problem?	Y	Y	Y
3	Is the primary decision maker specified?	Y	N	Y
4	Is the perspective of the model stated clearly?	Y	N	Y
5	Are the model inputs consistent with the stated perspective?	Y	UN	Y
6	Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	Y	Y	Y
7	Are the sources of the data used to develop the structure of the model specified?	Y	Y*	Y*
8	Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?	Y	Y*	Y*
9	Is there a clear definition of the options under evaluation?	Y	Y*	Y
10	Have all feasible and practical options been evaluated?	Y	N	Y
11	Is there justification for the exclusion of feasible options?	Y*	N	N
12	Is the chosen model type appropriate given the decision problem and specified casual relationships within the model?	Y	Y	Y
13	Is the time horizon of the model sufficient to reflect all important differences between the options?	Y	N	Y
14	Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?	Y	Y*	UN
15	Is the cycle length defined and justified in terms of the natural history of disease?	N	N	Y*
DATA				
16	Are the data identification methods transparent and appropriate given the objectives of the model?	Y	Y*	Y*
17	Where choices have been made between data sources are these justified appropriately?	Y	Y*	UN
18	Where expert opinion has been used are the methods described and justified?	N	N	N
19	Is the choice of baseline data described and justified?	N	N	N
20	Are transition probabilities calculated appropriately?	Y*	N	UN
21	Has a half-cycle correction been applied to both costs and outcomes?	N	N	N
22	If not, has the omission been justified?	N	N	N
23	Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?	Y	Y*	Y*
24	Are the costs incorporated into the model justified?	Y	Y	Y
25	Has the source for all costs been described?	Y	Y	Y
26	Have discount rates been described and justified given the target decision maker?	Y	Y	Y

27	Are the utilities incorporated into the model appropriate?	Y	Y	Y
28	Is the source of utility weights referenced?	Y	Y*	Y*
29	If data have been incorporated as distributions, has the choice of distributions for each parameter been described and justified?	Y*	N	N
30	If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	Y*	Y*	Y*
31	Has heterogeneity been dealt with by running the model separately for different sub-groups?	N	N	N
32	Have the results been compared with those of previous models and any differences in results explained?	Y*	Y*	N

Key: Y = yes, No = no, UN = unclear, N/A = not applicable and * = partially completed

Appendix X. Study characteristics of economics studies

Author Publication year Country	Aims, study design and patient group	Economic evaluation type, model, perspective & currency and price year	Costs and outcomes	Results
Derrett et al 2005 Country: UK	Aim: To assess costs and health status outcomes after ACI and mosaicplasty Study design: Cross-sectional retrospective study Patient group and numbers: - 53 ACI recipients - 20 mosaicplasty recipients - 22 ACI waiting list (ACI WL) recipients Mean age (% male): - ACI: 31.9 (53%) - Mosaicplasty: 34.9 (45%) - ACI WL: n/a (59%)	Type: Cost-utility analysis Model: None Perspective: Not stated Currency and price year: UK £ - 2003-2004 prices Time horizon: 2 years Discounting: None	Resource use and costs: Operations/treatments, arthroscopies, inpatient stay, day case and outpatient visits, MRI scans, histology and x-rays Outcomes: - Modified Cincinnati Knee Rating System - Pain Disability Index - EQ-5D-3L used to calculate QALYs Sensitivity analyses: One-way	Outcomes - EQ-5D means: - ACI = 0.64 - Mosaicplasty = 0.47 Costs: - ACI = £10,600 - Mosaicplasty = £7,948 ICER: - £16,349 cost per QALY
Gerlier et al 2010 Country: Belgium	Aim: To assess the cost-effectiveness of ACI with ChondroCelect	Type: Cost-utility analysis Model:	Resource use and costs: Reimbursed drugs, medical procedures	Outcomes - QALY means: - CC = 21.08 - Microfracture = 19.79

	(CC) compared with microfracture. Study design: Decision tree model Patient group: Adult patients < 50 years of age with symptomatic cartilage lesions of the femoral condyles who had not developed osteoarthritis	Decision tree Perspective: Global healthcare payer (public payer reimbursement plus possible patient co-payment) Currency and price year: Euro's € - 2008 prices Time horizon: 5 and 40 years Discounting: Costs - 3%; Effects - 1.5%	including ACI with CC and microfracture, consultations, hospitalisations and follow-up Outcomes: - Knee injury and Osteoarthritis Outcome Score (KOOS) - SF-36 collected from an RCT used to calculate QALYs Sensitivity analyses: One-way, two-way and probabilistic	Costs: - CC = €29,808 - Microfracture = €9,006 ICER: - €16,229 cost per QALY
Samuelson et al 2012 Country: USA	Aim: To assess the cost-effectiveness of ACI-C vs. ACI-P Study design: Decision tree model Patient group: Adult patients (30 years of age) with a focal chondral injury which satisfies the	Type: Cost-utility analysis Model: Decision tree Perspective: Not stated Currency and price year: US$ - price year not stated	Resource use and costs: Initial consultation, follow-up visits, surgical costs, ACI, physical therapy, medical equipment Outcomes: - Lysholm knee score - Utility values from literature used to calculate QALYs Sensitivity analyses:	Outcomes: - ACI-C = not stated - ACI-P = not stated Costs (total): - ACI-C = $66,940 - ACI-P = $66,752 ICER: - Not calculated

	conditions for ACI repair	Time horizon: 10 years Discounting: Costs – 3%; Effects – 3%	Threshold	
Koerber et al 2013 Country: Germany	Aim: To assess cost-effectiveness of mosaicplasty, ACI-P, ACI-C, MACI compared with microfracture Study design: Decision tree model Patient group: Patients aged 32 years with symptomatic, isolated cartilage defects and no contra indication.	Type: Cost-utility analysis Model: Decision tree Perspective: German statutory health insurance Currency and price year: Euros € - price year not stated Time horizon: 47 years Discounting: Costs – 3%; Effects – 3%	Resource use and costs: Surgical treatments, inpatient stays, outpatient visits, arthroscopy, revisions, GP visits, imaging, physiotherapy and medications Outcomes: - Utility values from literature used to calculate QALYs Sensitivity analyses: Probabilistic	Outcomes - QALY means: - Microfracture = 19.66 - Mosaicplasty = 19.47 - ACI-P = 19.76 - ACI-C = 19.79 - MACI = 19.80 Costs: - Microfracture = €13,445 - Mosaicplasty = €17,774 - ACI-P = €19,082 - ACI-C = €18,713 - MACI = €21,204 ICER: Cost per QALY gained in relation to Microfracture - Mosaicplasty is dominated by microfracture - ACI-P = €56,370 per QALY gained - ACI-C = €40,523 per QALY gained - MACI = €55,421 per QALY gained

Appendix XI. Annual transition probabilities

This section reports on the sources of the progression rates used in the Markov model. These transition probabilities were derived from the literature and in consultation with clinical experts. Most studies presented information in the form of success (progression) rates over a specified time period. These rates were converted to transition probabilities using the formula below, where r is the progression rate and t is time:

$$p_{transition} = 1\text{-}\exp\{-rt\}$$

Where progression rates were not available from the literature, we converted the probability of the event over a period of time to a constant rate using the formula below:

$$r = -[\ln(1-P)]/t$$

Patients receiving an ACI procedure - ACI (ACI) – 20 to 54 years (see Table 34)

Primary repair

Progression rates for people who progressed from primary repair to successful primary and to second repair were obtained from Saris et al[67] These authors provided information on a three-year failure rate of 3.9% for people who required re-operation of the same lesion. The three-year probability was obtained and then converted to a one-year transition probability of 0.01317 which was used in the model. They also reported a success rate of 83.0% over a three-year period. We assumed a three-year failure rate of 13.1% for people who had no further repair following the primary repair. Three-year probabilities were obtained for these latter two rates and then converted to one-year transition probabilities.

Successful primary

Progression rates for people who progressed from a successful primary repair to a second repair and for those that remain in that health state were based on information from Saris et al.[97] These authors reported a response rate of 87.5% over a two-year time period for people who had undergone a MACI implant. We assumed that 12.5% of the non-responders will move to the no further repair health state and of these 12.5% patients, we assumed that 10% of them will move from the successful primary to the second repair health state. Based on this information the following annual transition probabilities were derived: 0.93580, 0.05793 and 0.00627, respectively.

Second repair

The transitions required here include, people who have undergone a second repair that was successful, and people in whom it was unsuccessful, who do not have a further repair. Saris et al[67] reported a

three-year success rate for an initial procedure as 83.0%. Here, we assumed that the success rate in the second repair is the same as the success rate in the primary repair, if the second repair is the same as the first. For the people who have no further repair following the second repair, we derived a one-year transition probability of 0.06022. Here, we assumed that 17.0% of people will have no further repair over a three-year time period.

Successful second

Progression rates for people who progressed from a successful second repair to no further repair and for those that remain in that health state were based on information from Saris et al.[97] These authors reported a response rate of 87.5% over a two-year time period for people who had undergone a MACI implant. We assumed that 12.5% of people would move from the successful second to the no further repair health state. Based on this information the following annual transition probabilities were derived: 0.93541 and 0.06459, respectively.

Patients receiving an MF procedure – MF (MF) – 20 to 54 years (see Table 34)

Primary repair

People who received a primary repair can remain in the successful primary repair health state, have a second repair, or have no further repair and these values were obtained from Saris et al.[67] These authors reported that 11.5% of people who had undergone a primary repair required re-operation of the same lesions within 36 months. From this, we derived an annual transition probability of 0.03990 for those who require a second repair. The authors also reported that 62.0% of people will have a successful primary repair within 36 months. Taking account of the 62% who have initial success and the 11.5% who have a second repair within 3 year leaves 26.5% of the initial MF group that have no further repair in the first 3 years. We derived an annual transition probability of 0.09754 for people who receive no further repair.

Successful primary

Saris et al[97] reported on the percentage (68.1%) of people who responded to treatment at 2 years. We assumed that 31.9% of the non-responders will move to the no further repair health state and of these 31.9% patients, we assumed that 10% of them will move from the successful primary to the second repair health state. Based on this information the following annual transition probabilities were derived: 0.82825, 0.15567 and 0.01608 respectively.

Second repair

Saris and colleagues[67] reported a 62.0% success rate for people who had an initial primary repair over 36 months. Due to the paucity of information on the success rate for people receiving a second repair, we assumed the same percentage success for a second repair as for people who had a primary repair.

For the people who have no further repair following the second repair, we derived a one-year transition probability of 0.14730. Here, we assumed that 38.0% of people will have no further repair over a three-year time period.

Successful second

Saris et al[97] reported on the percentage (68.1%) of people who responded to treatment at 2 years. Here, we assumed that the percentage success for the second repair is the same for people who had a successful primary repair. We assumed 31.9% of people would receive no further repair. From this, we derived an annual transition probability of 0.17477 to represent those people who would receive no further repair. The annual transition probability of 0.82523 was derived to represent people who remained in a successful second repair health state.

Patients receiving MF after failed ACI - ACI (MF) – 20 to 54 years (see Table 34)

We report here the values for MF as a second procedure after ACI as these transition probabilities are different to ACI (ACI).

Second repair

People who had a second repair can have a successful second repair or do not receive a further repair. For those people who do not receive a further repair, we obtained this information from Vanlauwe et al.[40] These authors reported that for 16.4% of people who had the MF procedure following an ACI procedure, this procedure failed at five years. From this, we derived an annual transition probability of 0.03519 for people who do not receive a further repair. We assumed the remainder of the people would have a successful MF procedure following an ACI. From this, we derived an annual transition probability from second repair to successful second as 0.96481.

Successful second

Saris et al[97] reported that 68.1% of people responded to treatment at 2 years. We assumed that the percentage success for the second MF is as the first MF. We assumed 31.9% of people would receive no further repair. From this, we derived an annual transition probability of 0.17477 to represent those people who would not receive a further repair. The annual transition probability of 0.82523 was derived to represent people who remained in a successful second repair health state.

Patients receiving ACI after failed MF - MF (ACI) – 20 to 54 years (see Table 34)

We report here the values for ACI as a second procedure after MF as these transition probabilities are different to MF (MF).

Second repair

People who had a second repair can have a successful second repair. If the second repair is unsuccessful, we assumed that they do not receive a further repair. For those people who do not receive a further repair, we obtained this information from Biant et al.[76] These authors reported that for 30.9% of people who had the ACI procedure following an MF procedure, this procedure failed at ten year follow-up. From this, we derived an annual transition probability of 0.03629 for people who do not receive a further repair. We assumed the remainder of the people would have a successful ACI procedure following a MF. From this, we derived an annual transition probability from second repair to successful second as 0.96371.

Successful second

Saris et al[97] reported that 68.1% of people responded to treatment at 2 years. We assumed that the percentage success for the second repair is the same for people who had a successful primary repair (assuming that this repair was MF). We assumed 31.9% of people would receive no further repair. From this, we derived an annual transition probability of 0.17477 to represent those people who would not receive a further repair. The annual transition probability of 0.82523 was derived to represent people who remained in a successful second repair health state.

Patients 55+ years - all comparisons (see Table 35)

We report here only the transition probability values for the comparisons for patients aged 55+ years which are different to those for patients aged between 20 and 54 years.

Successful primary, successful second and no further repair

Information required for people who required a total knee replacement was obtained from Knutsen et al.[64] These authors reported that at the five-year follow-up, of the 40 patients who received an ACI and of the 40 patients who received a MF, nine patients in both groups failed the primary procedure and of these 9 patients, only one went on to have TKR (the same failure rate for both ACI and MF). For people who require a PKR following a failed primary repair, we assumed that this number would be the same as those receiving a TKR. From this information reported, we derived a one-year transition probability of 0.00505 to be used in the model for patients moving to the first TKR and first PKR health states from the successful primary, successful second and no further repair health states.

To estimate values for people who remain in the other health states (second repair, successful second and no further repair) the percentages for TKR and PKR were removed from the totals (i.e. from the success and failure rates) and the annual transition probabilities were re-estimated.

Patients 55+ years - all comparisons (see Table 36)

First total knee replacement

Gerlier and colleagues[102] reported information on the percentage success (99%) for people who had a total knee replacement. We assumed this success to be at five years following the initial TKR. We derived a transition probability of 0.99223 for patients moving from a first TKR to a successful first TKR. For the progression rates to further knee replacement, Dong and Buxton[118] reported that approximately 2% of people who had undergone their first total knee replacement required a total revision within 2-5 years. Here, we assumed 2% of people would require a revision procedure in 3.5 years. From this, we derived a one-year transition probability of 0.00576. We assumed that 1% of people would not receive a further knee replacement five-years following their first knee replacement.

First partial knee replacement

Due to the paucity of progression rates available from the literature for people who received a partial knee replacement, we used the percentage success and progression for people who received their first total knee replacement. We assumed a transition probability of 0.99223 for a successful first partial knee replacement, 0.00576 for people requiring a revision, and 0.00201 for people who receive no further knee replacement.

Successful first total knee replacement

People who received their primary knee replacement and was successful, we obtained this transition probability from Dong and Buxton. These authors provided information on the one-month probability of a successful knee replacement and to remain in normal health after the primary TKR. This one-month probability was converted into a one-year transition probability of 0.9737. Information on the progression to further knee replacement from a first knee replacement was obtained from Gerlier et al. These authors reported a 15% revision for people requiring further knee replacement, 15 years after the first total knee replacement. From this, we estimated an annual transition probability of 0.01078 for people requiring further revision. For people who receive no further knee replacement after the initial knee replacement, we derived an annual transition probability based on information on the percentage of successful and revision procedures reported in Dong and Buxton[118] and Gerlier et al.[102]

Successful partial knee replacement

We assumed the transition probabilities for people who had a partial knee replacement to be the same for people who had a total knee replacement. We assumed a one-year transition probability of 0.97307 for a successful PKR, a probability of 0.01078 for people requiring further revision and 0.01615 for people who receive no further knee replacement.

Further knee replacement

Gerlier and colleagues[102] reported a 90% success for people who have received a further knee replacement. We assumed this success to be at five years following the further knee replacement.

Also we assumed that 10% of people would receive no further knee replacement following the further knee replacement. We derived a transition probability of 0.02085 for people requiring no further knee replacements.

Successful further knee replacement

Gerlier and colleagues (2010) reported a 15% revision rate 15 years after successful total knee replacement. From this we derived a transition probability of 0.01078 for people requiring a further knee replacement. For people who remain in the successful further knee replacement health state following further knee replacement, Gerlier and colleagues (2010) reported a 90% success rate and we assumed this to be at five years. We derived an annual transition probability of 0.97307 for people remain in this health state. For people who had a successful further knee replacement and requiring no further knee replacement, we assumed this to be the same as a one-year transition probability of 0.01615 for successful first total knee replacement and requiring no further knee replacements.

Table 34. Annual transition probabilities – 20 to 54 years

From\to	Successful primary	Second repair	Successful second	No further repair		Successful primary	Second repair	Successful second	No further repair
	ACI (ACI)					MF (MF)			
Primary repair	0.94110	0.01317	-	0.04573		0.86256	0.03990	-	0.09754
Successful primary	0.93580	0.00627	-	0.05793		0.82825	0.01608	-	0.15567
Second repair	-	-	0.93978	0.06022		-	-	0.85270	0.14730
Successful second	-	-	0.93541	0.06459		-	-	0.82523	0.17477
No further repair	-	-	-	1.00000		-	-	-	1.00000
	MF (ACI)					ACI (MF)			
Primary repair	0.86256	0.03990	-	0.09754		0.94110	0.01317	-	0.04573
Successful primary	0.82825	0.01608	-	0.15567		0.93580	0.00627	-	0.05793
Second repair	-	-	0.96371	0.03629		-	-	0.96481	0.03519
Successful second	-	-	0.82523	0.17477		-	-	0.82523	0.17477
No further repair	-	-	-	1.00000		-	-	-	1.00000

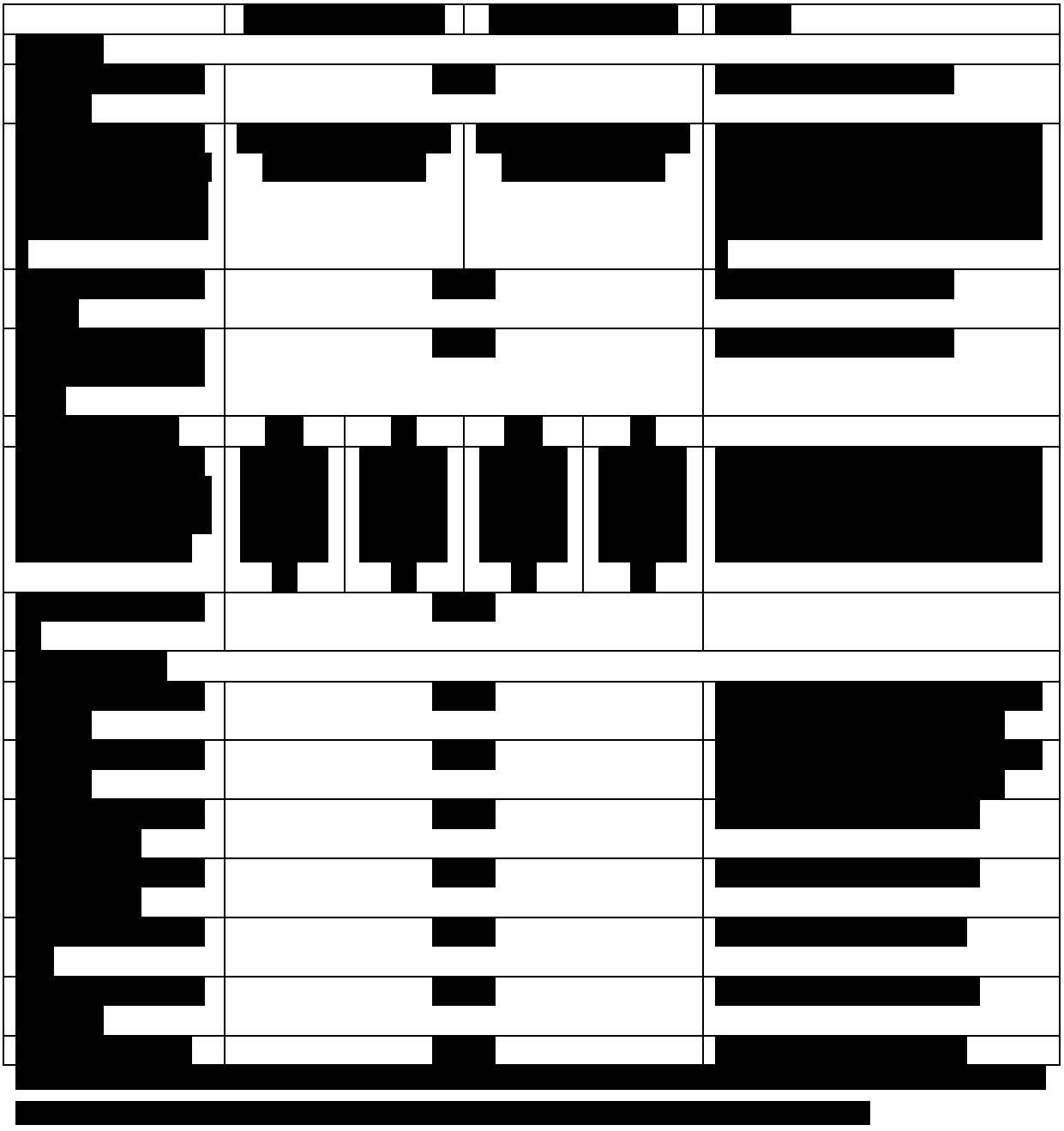
Table 35. Annual transition probabilities – 55 years +

From\ to	Successful primary	Second repair	Successful second	No further repair	First TKR	First PKR		Successful primary	Second repair	Successful second	No further repair	First TKR	First PKR
	ACI (ACI)							MF (MF)					
Successful primary	0.95180	0.00376	-	0.03434	0.00505	0.00505		0.84726	0.01608	-	0.12656	0.00505	0.00505
Second repair	-	-	0.93978	0.06022	-	-		-	-	0.85270	0.14730	-	-
Successful second	-	-	0.95167	0.03823	0.00505	0.00505		-	-	0.84489	0.14501	0.00505	0.00505
No further repair	-	-	-	0.98990	0.00505	0.00505		-	-	-	0.98990	0.00505	0.00505
	MF (ACI)							ACI (MF)					
Successful primary	0.84726	0.01608	-	0.12656	0.00505	0.00505		0.95180	0.00376	-	0.03434	0.00505	0.00505
Second repair	-	-	0.96371	0.03629	-	-		-	-	0.96481	0.03519	-	-
Successful second	-	-	0.84489	0.14501	0.00505	0.00505		-	-	0.84489	0.14501	0.00505	0.00505
No further repair	-	-	-	0.98990	0.00505	0.00505		-	-	-	0.98990	0.00505	0.00505

Table 36. Annual transition probabilities – 55 years + (for all scenarios)

From\to	Successful first TKR	Successful first PKR	Further KR	Successful further KR	No further KR
	All comparisons				
First TKR	0.99223	-	0.00576	-	0.00201
First PKR	-	0.99223	0.00576	-	0.00201
Successful first TKR	0.97307	-	0.01078	-	0.01615
Successful first PKR	-	0.97307	0.01078	-	0.01615
Further KR	-	-	-	0.97915	0.02085
Successful further KR	-	-	0.01078	0.97307	0.01615
No further KR	-	-	-	-	1.00000

[redacted]



[redacted]