*Health Technology Assessment* 2005; Vol. 9: No. 47

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December 2005


**Health Technology Assessment**
**NHS R&D HTA Programme**



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# Clinical and cost-effectiveness of autologous chondrocyte implantation for cartilage defects in knee joints: systematic review and economic evaluation

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**Declared competing interests of authors:** none

Published December 2005

This report should be referenced as follows:

Clar C, Cummins E, McIntyre L, Thomas S, Lamb J, Bain L, *et al*. Clinical and cost-effectiveness of autologous chondrocyte implantation for cartilage defects in knee joints: systematic review and economic evaluation. *Health Technol Assess* 2005;**9**(47).

*Health Technology Assessment* is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE and *Science Citation Index Expanded (SciSearch®)* and *Current Contents®*/Clinical Medicine.

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The research reported in this monograph was commissioned and funded by the HTA Programme on behalf of NICE as project number 03/65/01. The protocol was agreed in April 2004. The assessment report began editorial review in March 2005 and was accepted for publication in May 2005. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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ISSN 1366-5278



Published by Gray Publishing, Tunbridge Wells, Kent, on behalf of NCCHTA.
Printed on acid-free paper in the UK by St Edmundsbury Press Ltd, Bury St Edmunds, Suffolk.

# Abstract

## Clinical and cost-effectiveness of autologous chondrocyte implantation for cartilage defects in knee joints: systematic review and economic evaluation

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**Objective:** To support a review of the guidance issued by the National Institute for Health and Clinical Excellence (NICE) in December 2000 by examining the current clinical and cost-effectiveness evidence on autologous cartilage transplantation.
**Data sources:** Electronic databases.
**Review methods:** Evidence on clinical effectiveness was obtained from randomised trials, supplemented by data from selected observational studies for longer term results, and for the natural history of chondral lesions. Because of a lack of long-term results on outcomes such as later osteoarthritis and knee replacement, only illustrative modelling was done, using a range of assumptions that seemed reasonable, but were not evidence based.
**Results:** Four randomised controlled trials were included, as well as observational data from case series. The trials studied a total of 266 patients and the observational studies up to 101 patients. Two studies compared autologous chondrocyte implantation (ACI) with mosaicplasty, the third compared ACI with microfracture, and the fourth compared matrix-guided ACI (MACI®) with microfracture. Follow-up was 1 year in one study, and up to 3 years in the remaining three studies. The first trial of ACI versus mosaicplasty found that ACI gave better results than mosaicplasty at 1 year. Overall, 88% had excellent or good results with ACI versus 69% with mosaicplasty. About half of the biopsies after ACI showed hyaline cartilage. The second trial of ACI versus mosaicplasty found little difference in clinical outcomes at 2 years. Disappointingly, biopsies from the ACI group showed fibrocartilage rather than hyaline cartilage. The trial of ACI versus microfracture also found only small differences in outcomes at 2 years. Finally, the trial of MACI versus microfracture contained insufficient long-term results at present, but the study does show the feasibility of doing ACI by the MACI technique. It also suggested that after ACI, it takes 2 years for full-thickness cartilage to be produced. Reliable costs per quality-adjusted life-year (QALY) could not be calculated owing to the absence of necessary data. Simple short-term modelling suggests that the quality of life gain from ACI versus microfracture would have to be between 70 and 100% greater over 2 years for it to be more cost-effective within the £20,000–30,000 per QALY cost-effectiveness thresholds. However, if the quality of life gains could be maintained for a decade, increments relative to microfracture would only have to be 10–20% greater to justify additional treatment costs within the cost-effectiveness band indicated above. Follow-up from the trials so far has only been up to 2 years, with longer term outcomes being uncertain.
**Conclusions:** There is insufficient evidence at present to say that ACI is cost-effective compared with microfracture or mosaicplasty. Longer term outcomes are required. Economic modelling using some assumptions about long-term outcomes that seem reasonable suggests that ACI would be cost-effective

because it is more likely to produce hyaline cartilage, which is more likely to be durable and to prevent osteoarthritis in the longer term (e.g. 20 years). Further research is needed into earlier methods of predicting long-term results. Basic science research is also needed into factors that influence stem cells to become chondrocytes and to produce high-quality cartilage, as it may be possible to have more patients developing hyaline cartilage after microfracture. Study is also needed into cost-effective methods of rehabilitation and the effect of early mobilisation on cartilage growth.

# Contents

# Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

## Glossary

**Arthroscopy** Examination of the internal structure of a joint, by means of a fibre-optic scope. Surgical procedures may be carried out during this investigation. A form of keyhole surgery.

**Autologous** Tissue or cells from one's own body.

**Avascular necrosis** Damage to bone and cartilage due to a local loss of blood supply.

**Cartilage defect or chondral defect (or fracture)** Loss of cartilage lining the end of a bone; of variable thickness.

**Chondrocytes** Cells that produce cartilage.

**Collagen** Protein that gives cartilage its structure and strength. There are different types: type II predominates in hyaline cartilage; type I predominates in fibrocartilage.

**Condyle** Rounded end of femur which connects with tibia.

**Débridement** Removal of loose tissue debris from joint.

**Femur** Thigh bone. Femoral is the adjective, as in femoral condyle.

**Fibrocartilage** A form of cartilage found in some parts of the body such as the menisci of the knee, but not on the articular surface of joints. Composed mainly of type I collagen, and not as durable as hyaline cartilage.

**Hyaline cartilage** Cartilage that is usually found at the ends of bones, within a synovial joint.

**Osteochondral defect** Loss of cartilage and bone at a joint.

**Osteochondral fracture** Loss of cartilage and bone at a joint as a result of injury.

**Osteochondritis dissecans** Detached fragment of cartilage with or without bone, at a joint, arising spontaneously or as a result of injury.

**Osteoarthritis** A disease of joints in which there is evidence of cartilage loss and an accompanying reaction in bone.

## List of abbreviations

| | |
|---|---|
| ACI | autologous chondrocyte implantation |
| ARI | Aberdeen Royal Infirmary |
| BSR | British Society of Rheumatology |
| CaReS | Cartilage Regeneration System |
| CI | confidence interval |
| CPM | continuous passive motion |
| DES | Development Evaluation Service |
| EQ-5D | EuroQol 5 Dimensions |
| FDA | United States Food and Drug Administration |
| ICER | incremental cost-effectiveness ratio |
| ICRS | International Cartilage Repair Society |
| IKDC | International Knee Documentation Committee |
| ITT | intention-to-treat |
| MACI® | matrix-guided autologous chrondrocyte implantation |
| MRI | magnetic resonance imaging |
| NICE | National Institute for Health and Clinical Excellence |
| ns | not significant |
| OCD | osteochondritis dissecans |
| OCT | osteochondral cylinder transplantation |
| QALY | quality-adjusted life-year |
| QoL | quality of life |
| RCT | randomised controlled trial |
| RNOH | Royal National Orthopaedic Hospital |
| SD | standard deviation |
| SF-36 | Short Form 36 |
| TKA | total knee arthroplasty |
| TKR | total knee replacement |
| VAS | visual analogue scale |

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

# Executive summary

## Objective

To support a review of the guidance issued by the National Institute for Health and Clinical Excellence (NICE) in December 2000 by examining the current clinical and cost-effectiveness evidence on autologous cartilage transplantation.

## Proposed service and current methods

Autologous chondrocyte implantation (ACI) is a surgical approach used to treat full-thickness cartilage defects in knee joints. Small samples of normal cartilage with the cells that produce the cartilage (chondrocytes) are removed from the damaged joint. The cells are cultured in special laboratories to increase the number of cells and reimplanted a few weeks later into the areas of cartilage damage. The aim of this procedure is to restore normal hyaline cartilage to the ends of bones and thereby restore normal joint function. The procedure is used mainly for knee joints at present, but has been tried in other joints.

The current standard treatment of cartilage defects is by stimulating repair of the cartilage defect by cells from the underlying bone marrow, usually by the procedure known as microfracture. The hope is that the stem cells from the marrow will differentiate into chondrocytes that will then produce new cartilage. However, the cartilage they produce tends to be an inferior form known as fibrocartilage, which is not as good as the original hyaline cartilage.

Another technique used is called mosaicplasty (or autologous osteochondral cylinder transplantation), whereby cylindrical plugs of cartilage and bone are removed from less weight-bearing parts of the same knee, and transplanted into the damaged area. The problem of damage to the donor sites limits this procedure to smaller lesions.

The expected benefits of ACI consist of short-term relief of symptoms such as pain and long-term prevention of the development of osteoarthritis, and hence reduction in the need for later knee replacement.

## Epidemiology

There are no reliable estimates of the prevalence of cartilage defects in the knee. Lesions are most likely to arise in sportsmen and women as a result of injury, but are often a result of occupational injury. Up to 20% of those sustaining a haemarthrosis following a knee injury may have cartilage damage.

## Methods

This study is an update of a previous review published in this series. Evidence on clinical effectiveness was obtained from randomised trials, supplemented by data from selected observational studies for longer term results, and for the natural history of chondral lesions. Because of a lack of long-term results on outcomes such as later osteoarthritis and knee replacement, only illustrative modelling was done, using a range of assumptions that seemed reasonable, but were not evidence based.

## Results

### Number and quality of studies

Four randomised controlled trials were included, as well as observational data from case series. The trials studied a total of 266 patients and the observational studies up to 101 patients. Two studies compared ACI with mosaicplasty, the third compared ACI with microfracture, and the fourth compared matrix-guided ACI (MACI®) with microfracture. Follow-up was 1 year in one study, and up to 3 years in the remaining three studies. All studies had some methodological shortcomings.

### Summary of benefits

The first trial of ACI versus mosaicplasty found that ACI gave better results than mosaicplasty at 1 year. Overall, 88% had excellent or good results with ACI versus 69% with mosaicplasty. However, the benefit was statistically significant only in the

group with medial condylar (i.e. the inside of the leg) defects (just over half of the patients). The other groups (patella and lateral condyle) also did better with ACI, but numbers were too small for the results to be statistically significant. About half of the biopsies after ACI showed hyaline cartilage. The second trial of ACI versus mosaicplasty found little difference in clinical outcomes at 2 years. Disappointingly, biopsies from the ACI group showed fibrocartilage rather than hyaline cartilage. The trial of ACI versus microfracture also found only small differences in outcomes at 2 years. Finally, the trial of MACI versus microfracture contained insufficient long-term results at the time of this review, but the study does show the feasibility of doing ACI by the MACI technique. It also suggested that after ACI, it takes 2 years for full-thickness cartilage to be produced.

### Economic review

Reliable costs per quality-adjusted life-year (QALY) could not be calculated owing to the absence of necessary data. Simple short-term modelling suggests that the quality of life gain from ACI versus microfracture would have to be between 70 and 100% greater over 2 years for it to be more cost-effective within the £20,000–30,000 per QALY cost-effectiveness thresholds. However, if the quality of life gains could be maintained for a decade, increments relative to microfracture would only have to be 10–20% greater to justify additional treatment costs within the cost-effectiveness band indicated above.

### Limitations

The trials published in the literature at the time of this review all compare ACI with a different treatment. Therefore, data on each comparison are limited and no trial data are available for comparing ACI with no treatment. Follow-up from the trials so far has only been up to 2 years, with longer term outcomes being uncertain.

## Conclusions

There is insufficient evidence at present to say that ACI is cost-effective compared with microfracture or mosaicplasty. Longer term outcomes are required. In the absence of hard evidence, economic modelling using some assumptions about long-term outcomes that seem reasonable suggests that ACI would be cost-effective because it is more likely to produce hyaline cartilage, which is more likely to be durable and to prevent osteoarthritis in the longer term (e.g. 20 years). However, any results from modelling based on assumptions rather than evidence must be treated with caution.

## Recommendations for future research

The following areas are recommended for additional research.

- In addition to the need for longer term results referred to above, there is a need for study into earlier methods of predicting long-term results. Techniques such as modern methods of magnetic resonance imaging may be useful for assessing quality of cartilage.
- There is also a need for basic science research into the genes and molecules that influence stem cells to become chondrocytes and to produce high-quality cartilage. It may be possible to have more patients developing hyaline cartilage after microfracture. Substances such as cartilage growth factors may have a role.
- Methods of rehabilitation vary, with some centres encouraging weight bearing earlier than others. Research is needed into the most cost-effective method, and the effect of early mobilisation on cartilage growth.

# Chapter 1

# Aim of the review

In December 2000, the National Institute for Health and Clinical Excellence (NICE) issued Technology Appraisal Guidance number 16,[1] on autologous cartilage transplantation. 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 clinical trial, which, wherever possible, is randomised and adequately powered."

This decision was made because of a lack of high-quality evidence from randomised controlled trials (RCTs). The guidance noted the existence of 17 case series of different interventions but 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."

Most of these case series were of the 'before and after' variety. They are summarised in the previous HTA report by Jobanputra and colleagues.[2] Without control groups it is difficult to assess the effectiveness of a new procedure, relative either to the natural history of the condition, or to alternative interventions. Since then several trials have been carried out, and the evidence base has improved.

The aim of this review is to support a review of the guidance by examining the current evidence. The introduction in Chapter 2 is based on the corresponding section of the previous review. Chapter 3 reviews the evidence on clinical effectiveness. The full review of case series in the previous review has not been repeated. Readers are referred to the previous HTA monograph[2] if they wish details. The more important case series are used as a source of results of long-term follow-up, because the durations of the RCTs are as yet short. Shorter case series are not included.

The terminology has changed. The initial term of autologous cartilage transplantation is being 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. ACI will be used in this review.

# Chapter 2
# Background

## Underlying health problem

### Cartilage injuries

It is believed that injuries to knee hyaline cartilage predispose to osteoarthritis in later life and eventually to a requirement for knee replacement surgery because of increasing pain and disability. This is based on experimental observations that show that hyaline cartilage has a limited capacity for repair;[3,4] and epidemiological studies that show a relationship between knee injury and later development of osteoarthritis.[5] Normal hyaline cartilage provides a smooth surface at the ends of bones that allows virtually frictionless movement within a joint. Knee injuries, often as a result of sporting activity, may lead to bone, hyaline cartilage, meniscus (also called 'cartilage' by lay persons) and ligament damage (*Figure 1*). Injuries commonly occur in combination. Potentially this requires a range of surgical approaches for knee injuries. Loss of cartilage alone is referred to as a chondral fracture, whereas loss of bone and cartilage is known as an osteochondral fracture. Osteochondral fractures occur more commonly in adolescents as it appears that the plane of weakness at a joint, in adolescents, lies in bone rather than at the junction of cartilage and bone.[6,7]

### Aetiology, diagnosis and natural history

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 diseased menisci.[9] Spontaneous loss of a fragment of bone and cartilage from a joint occurs in OCD. However, this term is not always applied consistently and may be used to describe bone and cartilage loss due to injury. In young people the most common cause of hyaline cartilage damage is sporting injuries. Aroen and colleagues[10] report the causes of injury in patients having knee arthroscopy in Norway over a 6-month period. 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.

There is limited evidence on the natural history of hyaline cartilage lesions or chondral fractures that follow injury in humans. Cartilage lacks a nerve supply and isolated cartilage damage does not directly cause pain. Therefore a proportion of patients with significant hyaline cartilage damage

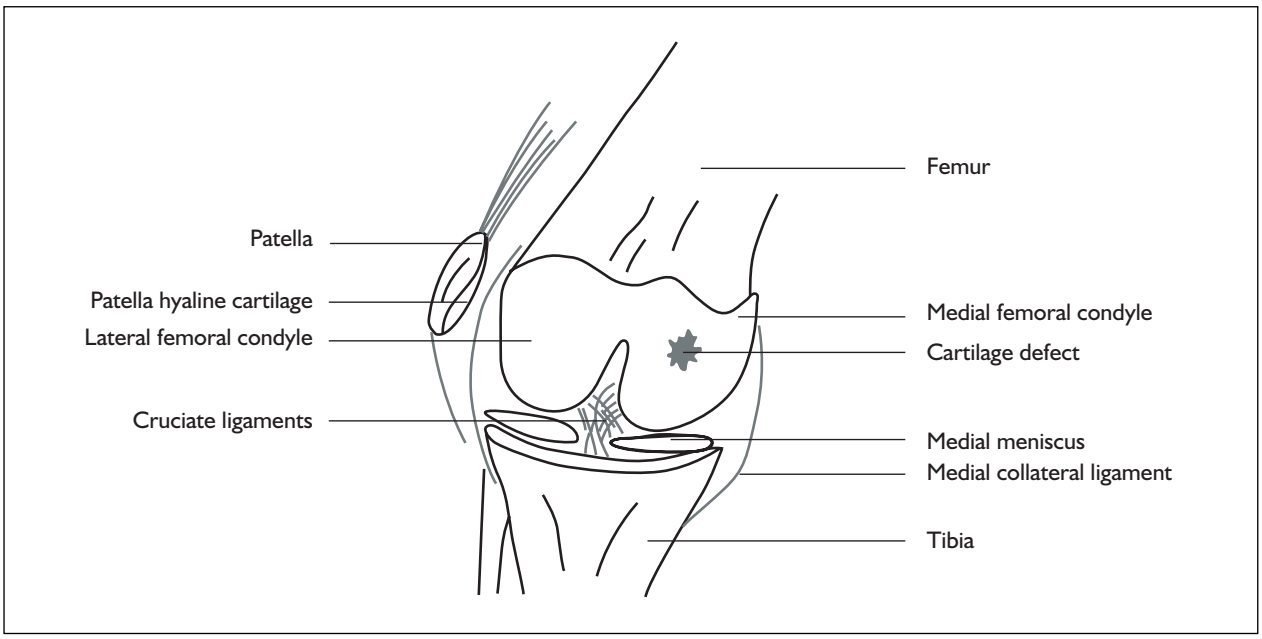


***FIGURE 1*** *Anatomy of a knee joint*

do not experience pain and may not experience any other symptoms associated with knee injury. Those experiencing symptoms with loss of hyaline cartilage of full thickness have symptoms similar to those of a meniscal tear.[11] Patients complain of knee pain, knee swelling, joint locking (i.e. a joint becomes stuck in one position) and giving way of the joint. Knee injuries of various sorts may cause a chondral or an osteochondral defect; for example, a direct shearing force on the medial or lateral femoral condyles due to a heavy fall on a bent knee, or a direct impact, such as a kick on a bent knee, or as a result of patellar dislocation. Rotary forces on the knee while weight bearing, for example a sudden or unintended change in direction in a skier or footballer, may also produce similar injuries.[5,12]

Cartilage defects are usually diagnosed at arthroscopy,[13] although they may be seen on magnetic resonance imaging (MRI). Osteochondral fractures, because they involve bone, may be seen on X-rays. OCD resembles osteochondral fractures in that a segment of joint cartilage and some bone becomes detached from the joint surface. Characteristically, OCD is a concentric lesion that involves the medial femoral condyle in a knee. It develops spontaneously, without a precipitating injury, often during the second decade of life.[14] Some believe that OCD arises as a result of localised avascular necrosis (loss of blood supply) of the subchondral bone causing separation of a fragment of bone and cartilage.[15] Long-term studies of OCD provide the only source of information on the likely natural history of cartilage defects in a knee joint. For example, Linden found that 55% of adults, but no children, went on to develop severe osteoarthritis. In this study 58 patients were followed for an average of 33 years.[16] Linden suggested that tissue repair was more effective in children and that osteoarthritis occurs in OCD some 10 years earlier in life than in osteoarthritis due to other causes.[16] However, many adults are symptom free for up to 20 years before they develop evidence of osteoarthritis. Messner and Maletius[17] reported on the outcomes in 28 young athletes (mean age 25, range 14–38 years) after severe (grade 2 or 3) chondral damage. With no treatment, 14 years later ten had excellent function, 12 had good function and six had problems; 21 had returned to activity. Symptoms such as pain and locking had resolved in most cases. However, the radiological picture was not as good as the clinical one, with narrowing of joint space common, suggesting that osteoarthritis was developing despite the relative lack of symptoms at that stage of follow-up.

Prakash and Learmonth[18] studied 15 knees in 12 patients (aged 14–38 years) with isolated osteochondral defect on a femoral condyle, not treated surgically. Follow-up at a mean of 9 years (range 1–23 years) showed that the Lysholm score (see Appendix 1 for details of scoring systems) improved with time. The results were better for those under 18 years at diagnosis, with none of the lesions diagnosed in children showing signs of osteoarthritis on MRI scan compared with six of the eight lesions diagnosed in adulthood.

Shelbourne and colleagues[19] reported on a group of 124 patients who had been noted to have an articular cartilage defect (Outerbridge grade 3 or 4; see Appendix 2) while having anterior cruciate ligament repair. The cartilage defects were not treated. One-hundred and one of them were followed up for more than 2 years (mean follow-up was 8.7 years) and compared with a matched group who had not had cartilage defects. There was no difference in stability, range of movements, strength or activity levels. There was some reduction in total modified Noyes score (see Appendix 1 for details), but both groups had high scores: the no defect group had a mean score of 96 out of 100, the cartilage defect groups 94 for medial condyle and 93 for lateral condyle. Hence, the natural history of chondral defects shows good symptomatic recovery and return to activity. This does not mean that normal cartilage has regenerated, but implies that fibrocartilage can provide a satisfactory result in the medium term.

However, the timescale for assessment may be critical. A mean follow-up of almost 9 years, as in the above study, is long compared with many other disease/intervention studies, but may not be long in the case of cartilage defects that eventually lead to osteoarthritis.

Defects in hyaline cartilage may repair by two main mechanisms: first, intrinsic repair by which tissue regenerates from cartilage alone; and second, extrinsic repair in which other cell types, for example synovial or bone marrow cells, contribute to repair (reviewed in Stockwell[20]). Only the latter mechanism appears to be effective. Intrinsic repair mechanisms may be ineffective owing to the limited capacity of cells in hyaline cartilage (chondrocytes) to respond to large defects arising from injury or surgery. The chondrocytes are embedded in the mesh of collagen fibres and proteoglycans that they produce. Thus, partial-thickness cartilage defects in joints rarely heal because bone marrow precursor cells cannot contribute to repair. Cells

with a capacity to repair cartilage may come from bone marrow, synovial tissues[21] or perhaps synovial fluid, and the periosteal lining of bone. Healing often occurs by formation of fibrocartilage, a tissue that is softer and less durable than hyaline cartilage.[22]

## Prevalence and incidence

The prevalence or incidence of hyaline cartilage damage in knee joints is not known. This is partly because cartilage defects may arise from a variety of direct injuries. Alternatively, they may arise indirectly from another knee injury, many months or years after the primary insult. In addition, patients with knee symptoms due to cartilage defects may present to a variety of medical practitioners, and may be evaluated with differing diagnostic approaches. Patients with serious knee symptoms may be investigated by an arthroscopic examination of the knee joint. Data from a large database of arthroscopies show that full-thickness loss of cartilage, in those under the age of 40, accounts for 5% of all procedures.[23] Unfortunately, prevalence and incidence cannot be estimated from this study, as precise patient numbers are not given. In acute knee injuries where there is a haemarthrosis (bleeding into the joint) around 20% of knees show cartilage surface defects (chondral fractures), often with other damage within the knee such as lesions of the anterior cruciate ligament and of menisci.[24] The incidence of OCD, in comparison with injury-related cartilage damage, is low and lies between 30 and 70 patients per 500,000 population, primarily in those between the ages of 10 and 30 years.[25]

Two Norwegian studies found that between 7 and 11% of patients undergoing arthroscopy may be eligible for ACI, assuming that the criteria are age under 45 years and single full-thickness defect over 2 cm.[10,26]

The age cut-off around 45–50 years is applied for two reasons. First, cartilage repair is better in younger patients; second, knee replacement is undesirable in younger people, partly because it is accompanied by some loss of function which restricts activities, and partly because of concern that knee replacements will not last for the full life of the patient, and that the replacement will need to be replaced – a more difficult and expensive operation.

There have been some studies reporting long-term follow-up of knee replacements in younger people, but there are two problems with these for the present purposes. First, 'long term' may only be 15 years. Ranawat and colleagues report that in 112 patients followed for 15 years, 94% had good clinical results.[27] Duffy and colleagues,[28] with a mean follow-up of 13 years (minimum 10 years) in 54 patients aged under 55 years at joint replacement, reported only two revisions. Survival without revision was estimated to be 95% at 15 years. These results are good, but the mean age of the group of patients with chondral damage is 32 years (with some as young as 18) and they would need far longer survival of knee prostheses if they were to avoid the need for second replacements. Second, many of the patients in these studies do not have osteoarthritis (which is what the group with chondral defects will be at risk of) but inflammatory arthritis, mainly rheumatoid. Patients with rheumatoid arthritis will have problems with other joints and will be less active. Their prostheses are therefore likely to last much longer. There are studies on total knee arthroplasty (TKA) under the age of 55 with osteoarthritis, but follow-up is shorter. Stern and colleagues reported 100% success, but at only 6 years' follow-up.[29]

Some reports suggest that isolated cartilage damage is relatively uncommon; occurring in only eight patients in a series of over 1000 arthroscopies.[30] However, significant cartilage injury, as judged by microscopic appearances of cartilage over areas of 'bone bruising' or bony contusion seen on MRI, appears to be fairly common.[31] In these cases there is frequently no abnormality of the cartilage surface if the joint is examined by arthroscopy soon after injury. However with time, patients who have sustained a bone bruise seen on an initial MRI show evidence of cartilage loss in around 50% of cases with follow-up MRI.[32] These data suggest that cartilage damage may frequently go unrecognised, especially as conventional MRI scans are relatively insensitive in detecting cartilage defects compared with arthroscopy.[33]

## Impact on quality of life

Knee injuries requiring hospital attention are associated with a significant impact on quality of life. For example, scores on a Short Form 36 (SF-36) health questionnaire indicate that physical functioning, role limitations due to physical problems, pain and social functioning are all significantly worse than scores for the general population.[34] For those with advanced knee disease requiring joint replacement surgery the impact on quality of life, rated by the EuroQoL index, is as low as 0.359 (where 1.00 represents perfect health).[35] In professional sportsmen and women,

and in individuals who have physically demanding jobs, cartilage injuries, in addition to limiting quality of life, may lead to loss of employment.

## Current service provision

### Treatment options

There has been no uniform approach to managing hyaline cartilage defects in knees. The majority of defects are identified at arthroscopy. Common treatments have included:

- lavage, wherein the knee is washed out with up to 3 litres of saline
- débridement, where surgeons trim loose tissue flaps in the belief that such tissues might be contributing to patient symptoms.

Evidence for the benefits of lavage is weak. In a single-author trial from Wales, Hubbard[36] randomised 76 patients to lavage alone or lavage plus débridement. At 1-year follow-up, 32 out of 40 allocated to débridement and lavage were pain free compared with five out of 36 allocated to lavage alone. This study can be criticised on the grounds that all outcome assessment was done by the operator rather than someone blinded to the intervention, but it provides useful longer term data showing that at 5 years only 19 out of 32 of the débridement group and three out of 26 of the lavage-alone group were pain free.

The best trial was by Mosely and colleagues.[37] This was a randomised trial with concealed allocation and blinded outcome assessment, with three arms: lavage alone, lavage plus débridement, and a placebo arm in which patients had a simulation procedure without insertion of the arthroscope into the knee. At 2 years there was no difference in pain among the groups, suggesting that neither lavage nor débridement is effective. However, this study was done in patients with osteoarthritis, and may not be relevant to those with only cartilage injury.

Other surgical procedures used to treat cartilage defects include marrow stimulation techniques, various tissue grafts from outside the joint, for example rib or periosteum grafts, and grafts of normal cartilage cores from within an affected joint (mosaicplasty). These fall into two groups:

- stimulation of repair, for example by methods to allow entry of marrow cells into the cartilage defect; the usual method is now called microfracture
- replacement of cartilage, by mosaicplasty or ACI.

A brief description of key techniques is given in *Table 1*. In addition to surgical interventions, post-operative management of patients varies considerably. For example, there is variation in regimens for weight bearing or physiotherapy techniques, including the post-operative use of continuous passive motion (CPM). In CPM the affected knee is subjected to continuous involuntary movements, by a mechanical device, to provide stimulation to improve range of motion. This also provides a mechanical stimulus to knee structures to promote healing. It is unknown whether cartilage healing is promoted by CPM in humans. A systematic review by Kirschner[48] found that the available evidence was inconclusive. The present report is not concerned with non-operative management and medical therapies. The focus is on surgical management, while acknowledging that variation in post-operative rehabilitation may influence the outcomes of any surgical approach. In general, post-operative rehabilitation is now shorter, with earlier mobilisation and weight bearing.

Most reports of treatment of knee hyaline cartilage defects describe a series of cases without historical or concurrent controls. Many studies describe patients with established knee osteoarthritis with changes on X-rays, rather than patients with localised cartilage loss following knee injury. Such patients are believed to be unsuitable for ACI (see below). Not surprisingly, in view of the uncertainties regarding the management of cartilage defects, surveys of surgeons showed considerable variation in diagnostic and surgical approaches. A survey describing responses from 255 German surgeons indicated that most surgeons favour marrow stimulation techniques as the primary approach to managing cartilage defects. Other treatments appear to be rarely used.[49]

### Requirements for ACI

To treat a patient with ACI an orthopaedic surgeon needs skills in the assessment and treatment of knee injuries, including arthroscopic surgery. In addition, special training is required in the techniques of ACI. Three commercial agencies, Genzyme, BBraun and Verigen Transplantation Services, provide services to support ACI in the UK. Two also provide training for orthopaedic surgeons with an interest in this area. All agencies providing commercial services need to prepare cells to an appropriate standard. This is considered in more detail below.

***TABLE 1*** *Treatment options for cartilage defects in knee joints*

| Method | Description and purpose |
|---|---|
| Knee washout | To remove intra-articular debris and potentially harmful enzymes, and to reduce inflammatory reactions. Arthroscopic or percutaneous approaches |
| Arthroscopic débridement | Usually refers to removal of loose cartilage tissue surrounding a cartilage defect accompanied by a knee washout[37] |
| Marrow stimulation techniques | Includes 'abrasion arthroplasty', subchondral drilling, microfracture and 'spongialisation'. Used for full-thickness, or near full-thickness, cartilage defects. Defects edges are debrided and the base of a defect (subchondral bone) is breached in various ways to allow access for bone marrow cells, with the idea of stimulating healing. A motor burr (abrasion arthroplasty[38]), a drill, a surgical pick, or more radically subchondral bone resection (spongialisation[39]) can be used. Microfracture now seems to be the standard method[40] |
| Mesenchymal cell grafts | Periosteum (a delicate cell layer adjacent to, and overlying, bone) and perichondrium (cell layer around ribs) are capable of producing hyaline cartilage. Grafts of these tissues have been used in knee cartilage defects,[41,42] but are now little used |
| Woven carbon fibre grafts | Artificial fibre discs, e.g. of carbon, silicon or collagen, may be used to fill in cartilage surface defects[43] |
| Mosaicplasty | Cylinders of normal cartilage and bone (~4.5 mm diameter), from 'non-weight-bearing' areas of an affected knee are removed and placed into cartilage defects at a single surgical procedure. Also known as autografts. Results in formation of a patchwork or mosaic.[44] Usually restricted to defects $<2$ cm$^2$ in diameter. Contraindicated in established osteoarthritis[45] |
| Osteochondral grafts | Grafts of mature cartilage, with a supporting layer of bone (2–10 mm thick), fresh or frozen, and obtained from a donor (allografts). Usually used for compound injuries where restoration of bone is a priority.[46] Not considered an option in this review because of the fear of cross-infection such as CJD |
| Paste grafts | Cartilage and bone harvested from a non-weight-bearing area of an affected knee (as for mosaicplasty) are formed into a paste and packed into a cartilage defect[47] |
| ACI | Autografts of cartilage, from 'non-weight-bearing' areas of an affected knee, are removed at arthroscopy. Grafts of 200–300 mg, an area of ~0.5 × 1 cm, are treated in a laboratory to extract chondrocytes. Cells are cultured for 3–5 weeks to expand the cell population, and are used in a planned second operation requiring open-knee surgery. A cell suspension is injected into a debrided cartilage defect beneath a specially created lid of periosteum or artificial collagen. The rim of the lid is sutured in place and sealed with fibrin glue |
| Matrix-guided ACI | In this form of ACI, the cells are loaded on to a collagen membrane, which avoids the need for the periosteal cap |

CJD, Creutzfeldt–Jakob disease.

# Description of new intervention

## ACI: indication, diffusion and potential costs

Ideally, patients should have a symptomatic cartilage defect of surface area 2–10 cm$^2$ that may include fissuring, fragmentation or loss of surface cartilage, but not necessarily full-thickness loss of cartilage (Outerbridge[50] grade III or more, Appendix 2). Patients are usually aged between 15 and 55 years and radiographic evidence of osteoarthritis should be absent. This means that the knee joint space should be near normal and new bone formation (osteophytes), a feature of osteoarthritis, should not be seen.[51] A variety of other relative or absolute contraindications has been suggested, including disease in the patella and multiple small cartilage lesions. In practice, however, patients with defects of the patella or multiple defects have had ACI. It is not necessarily only a second line treatment: many patients treated with ACI have not been treated with any other surgical procedure before ACI.[52]

The US Food and Drug Administration (FDA) granted a 'biologics' licence to Genzyme Tissue Repair in August 1997 for the commercial use of ACI.[53] The FDA had stipulated a requirement for postmarketing studies to confirm data and to assess long-term clinical outcomes. In a press

release Genzyme Corporation indicated that two multicentre randomised studies involving more than 500 patients were planned.[53] It was proposed to compare ACI with marrow stimulation techniques or periosteal grafting. Both studies were expected to report in 2003. However, Genzyme concluded that they could not run large enough RCTs and the FDA revised the labelled indication to second line, saying:

> "Carticel is indicated for the repair of symptomatic, cartilaginous defects of the femoral condyle, caused by acute or repetitive trauma, in patients who have had an inadequate response to a prior arthroscopic or other surgical procedure."

Some health insurance agencies in the USA reimburse the surgical expenses connected with ACI. However, despite a degree of consensus on the appropriate uses of ACI, there is evidence ACI is being used for conditions in which it is not indicated.[54]

In the UK several procedures have been carried out by a small number of interested surgeons. One company has a register of UK surgeons trained in the procedure, but the total number of procedures carried out in the UK is unknown. Worldwide, hundreds of surgeons contribute patient information to a database maintained by Genzyme Tissue Repair. Genzyme promotes chondrocyte implantation through its tissue repair section, Carticel.[SM] The majority of surgeons using Carticel services are based in the USA, Germany and England. The agencies providing a service for chondrocyte transplantation require skills in the culture of cartilage cells in a laboratory, to an appropriate standard. Currently, Verigen Transplantation Services International also offers this service, through a facility in Copenhagen. Co-don, a biotechnology firm, provides this service for the German market.[55] In addition, in-house methods for chondrocyte culture have been developed and are in use at the Robert Jones and Agnes Hunt Orthopaedic and District NHS Trust (RJAH) in Oswestry.[56] A Swedish team also has in-house expertise and is the largest single group with experience in ACI.[57]

## ACI: surgical procedure, post-operative care and follow-up

ACI surgery is briefly described in *Table 1*. Minas and Peterson give a more detailed description.[57] At a first arthroscopy, in preparation for ACI, a careful assessment of cartilage damage including the quality of surrounding cartilage, and of other intra-articular structures and joint stability, is made. Healthy cartilage, surrounding the cartilage defect, is needed so that a periosteal flap might be sutured over the defect to form a lid, but this is being replaced by collagen scaffolds. Cartilage biopsies are taken to provide cells for culture. Biopsies yield approximately $2–3 \times 10^5$ cells that yield, after culture, up to 20 million cells. Cartilage biopsies are taken from areas of the knee joint that are not thought to be subject to weight-bearing load. Additional surgical treatment for concomitant injuries, for example to ligaments or menisci, or other knee problems such as abnormal tracking of the kneecap, may also be required. Such treatments may be done at the time of ACI or at other additional operations.

After cell culture, at chondrocyte implantation, the knee joint is accessed by open arthrotomy or arthroscopy and the cartilage defect is debrided thoroughly to healthy cartilage. It is believed that contaminating cells from bone marrow increase the risk of fibrocartilage formation. Therefore, care is taken to achieve a contained defect and to avoid penetrating the subchondral plate so that bone marrow cells are not able to enter the defect. Originally, periosteum tissue was procured from the proximal end of the tibia. This delicate tissue can be used to form a lid over the cartilage defect. It is secured over the cartilage defect by suturing through normal cartilage or adjacent tissues (such as synovium) surrounding the defect. A watertight drum is created, using a fibrin sealant if necessary. Fibrin is made from a unit of the patient's blood collected pre-operatively. Cultured chondrocytes, prepared as a cell suspension, are then injected under the periosteal patch.

Verigen Transplantation Service International (VTSI) has introduced two modifications to this technique. First, instead of using periosteum to cover the cartilage defect, their method uses a highly purified porcine collagen membrane made of collagen types I and III. This has the advantage of not requiring a second incision to procure periosteum when cells are implanted. A second modification is the use of cells cultured within a biological matrix. In this technique, called MACI®, cultured chondrocytes are seeded onto a purified biological collagen membrane. This is then available for implantation. The advantages are that a piece of tissue, housing cultured and viable chondrocytes, can be cut to size and glued into the cartilage defect, the side-effects associated with the periosteal patch are avoided, and there can be a shorter operation and hospital stay than with an open operation.

In other systems, such as CaReS (Cartilage Regeneration System), the cells are actually grown in a collagen gel.[58] In Hyalograft, the cells are grown in a three-dimensional hyaluronan scaffold.[59]

Cartilage requires many months to heal. This means that the results of any attempt at repair should be assessed after many months, preferably many years, especially if the goal of therapy is to avert the risk of joint failure. Minas and Peterson[51] describe three key stages of cartilage repair. These include cellular proliferation (up to 6 weeks), transition (7–26 weeks) and remodelling (beyond 27 weeks). Since newly formed reparative tissue is vulnerable to mechanical damage in the early post-operative period, rehabilitation is prolonged. Patients in early studies were treated with CPM within 24 hours of surgery for 6–8 hours per day for the first 6 weeks after surgery. Crutches were used for the first 6 weeks. Thereafter, weight bearing was permitted gradually to achieve full body weight at 12 weeks. Nowadays, rehabilitation is much shorter (see Chapter 3). Running is not permitted until after 9 months and most patients use crutches or a walking cane for 4–5 months.

A key implication of the slow repair process is that the optimum result may not be obtained for 2 years, so earlier comparison against other techniques could underestimate the success of ACI.

The costs of the cells vary according to volume of service, and no doubt depend to some extent on local deals with manufacturers. Prices may be for a package including training, shipping costs, and so on. The cells are expensive, with figures such as £4000 from BBraun and £3500 from Verigen. It has been indicated that there can be economies of scale for centres doing a lot of ACI.

## Quality assurance

Use of autologous tissue to repair cartilage avoids the potential for graft rejection that may arise with foreign tissues. It also reduces the hazards of viral transmission. However, laboratory culture of cells for later injection into patients creates other potential hazards. For example, there is a potential for infecting tissues in the laboratory, a possibility of failure to cultivate cells adequately, cell death in the laboratory, such as when freezing and thawing cells, and errors in labelling samples during acquisition, storage or implantation of tissues. Adequate standards for quality assurance are essential to minimise such hazards. Genzyme is the largest provider of this service worldwide and adheres to a quality assurance programme stipulated by the FDA. Based on a series of 304 orders of ACI, only one order was not fulfilled during 1996 (0.33%), but errors in processing "that did not impact on patient safety" were identified in 5% of cell processing activities.[60]

The regulatory situation in the UK is that products engineered from human tissue fall within the remit of the Medicines and Healthcare Products Regulatory Agency (MHRA), which was formed by the merger of the Medicines Control Agency and the Medical Devices Agency. The UK Government's establishment of this agency was considered to be partly because of concern about how to regulate 'borderline technologies' such as ACI, which are neither drugs nor devices, since at present they are not covered by procedures for market approval. It is expected that new European legislation will be introduced.[61]

# Chapter 3

# Clinical effectiveness

## Methods

### Search strategy

Papers were identified using the following search strategies:

- Electronic databases searched included MEDLINE (Ovid, 2000 to June 2004 for ACI search, 1996 to June 2004 for search of other techniques for repairing cartilage defects, and for economic search, 1966 to June 2004 for quality of life search), EMBASE (Ovid, 2000 to June 2004 for ACI search, 1996 to June 2004 for search of other techniques for repairing cartilage defects, and for economic search, 1980 to June 2004 for quality of life search), Sports Discus (2000 to 2004), The Cochrane Library (Issue 2, 2004), NHS Centre for Reviews and Dissemination Databases (May 2004), BIOSIS (2000 to 6 June 2004), EBSCO Biomedical Reference Collection (6 June 2004), HSTAT (6 June 2004), Science Citation Index (6 June 2004), Social Science Citation Index (6 June 2004) and Department of Health Research Findings Register ReFeR (6 June 2004). Medical Subject Headings (MeSH) and keywords encompassing cartilage diseases, chondrocytes, knee diseases, knee injury, costs, quality of life, autologous implantation and other repair techniques were sought. Details of the search strategies used are shown in Appendix 3.
- Databases of ongoing trials: www.controlled-trials.com (June 2004) and National Research Register (6 June 2004) were searched.
- Abstracts from the meetings of the American Academy of Orthopedic Surgeons (2000–2004) were searched.
- Broad Internet searches were performed using a metasearch engine (Dogpile).
- Reference lists of relevant studies and reviews identified were scanned, as well as studies reported in industry submissions to NICE.

### Inclusion and exclusion criteria

Studies were included if they were prospective controlled trials (RCTs) of ACI for localised defects of the knee, in comparison to any other or no treatment, in any patient group. Abstracts were included provided that relevant data were shown and that publication of the abstract was not superseded by publication as a full paper. Long-term (follow-up of at least 2 years) uncontrolled studies of interventions for localised knee defects, or natural history, were also included to enable a comparison of long-term outcomes across studies. Studies in all languages were included.

### Data extraction

Two reviewers extracted data regarding study design and characteristics, details of the intervention, and patient characteristics and outcomes into a specially designed form, which was piloted before use. Differences in data extraction were resolved by discussion, referring back to the original paper. Data extraction for German studies was done by one reviewer only.

### Quality assessment

To assess the quality of controlled trials, the following criteria were assessed: method of randomisation, allocation concealment, handling of missing data/complete description of losses to follow-up, intention-to-treat (ITT) analysis, power calculation, blinding of patients (if possible), blinding of carers, blinding of outcome assessors, comparable timing of outcome assessment between groups, comparable post-operative rehabilitation between groups, specification of eligibility criteria, similarity at baseline with respect to prognostic factors, presentation of point estimates and measure of variability for primary outcome measure, and sponsoring by manufacturer.

Overall study quality was rated as follows: A (all quality criteria met), B (one or more of the quality criteria only partially met, or C (one or more criteria not met).

## Results

### Search results

Five RCTs comparing ACI with another type of cartilage repair surgery were identified.[58,62–65] However, one of the trials[58] compared two different forms of ACI (standard ACI and ACI with chondrocytes grown in a special collagen gel) and is therefore not relevant to the question of whether ACI is superior to other types of cartilage repair interventions. This also applies for an

ongoing trial of ACI versus MACI described in the submission by the Royal National Orthopaedic Hospital (RNOH).

# Trials

## Bentley and colleagues (2003)[64]

### *Description and quality of study*

This RCT compared ACI with mosaicplasty for the repair of articular defects of mixed aetiology and site. Consecutive patients with osteochondral or chondral defects of more than 1 cm in diameter were randomised and assessed 1 year post-operatively using the Cincinatti Rating Scale. There was no a priori sample size calculation. Most patients (94%) had had previous knee surgery, but no details were given of the type of operations or outcome of the initial operation (no benefit or initial benefit and if initial benefit, for how long). Treatment groups appeared dissimilar at baseline with respect to defect site and aetiology, but the statistical significance of baseline characteristics was not reported. No information was provided on the level of function or fitness of the patients at baseline, whether they were employed or unable to work, and whether they had been active sportspersons or had had a sedentary lifestyle. The experience of the surgeons in performing ACI was not mentioned, nor was the number involved. Two different types of flap were used to seal the defect (periostium in six patients and a porcine collagen membrane in 46 patients). It was not reported whether any concomitant surgery was carried out. Rehabilitation programmes were the same for both treatment groups. It was not reported whether the assessor of the outcome at 1 year was blinded to treatment allocation. Patients were also assessed using the Stanmore functional rating system, but although the authors state that the results were similar to the Cincinnati ratings, results using the Stanmore system were not reported. Subgroups of patients were analysed according to cartilage defect site, but it was not stated whether these analyses were planned or post hoc analyses. Adverse effects were not reported by treatment group and were not reported in detail. The authors of the trial stated that they will receive or have received benefits from a commercial party related directly or indirectly to the subject of the article.

### *Participants*

Bentley and colleagues recruited 100 consecutive patients with symptomatic lesions of the articular cartilage in the knee suitable for cartilage repair. Patients' knees had to have an osteochondral or a chondral defect of more than 1 cm in diameter in a joint that was otherwise biomechanically normal and free from inflammatory disease. Surgery was considered appropriate for patients with persistent pain and reduction in activities, but no details were given of the level of reduction required before surgery. Patients were aged between 16 and 49 years (mean age 31.3 years), 57% were male and the mean duration of symptoms was 7.2 years. No details were given of the baseline level of function of the study participants. All participants had previously had arthroscopy, 94% had previous surgery and the mean number of further operations was 1.5. No details were given of the types of previous operations. Patients had cartilage defects of varying aetiologies: trauma 46%, OCD 19%, chondromalacia patellae 14%, and other, probably post-traumatic 21%. Defects ranged in size from 1 to 12.2 $cm^2$ (mean 4.66 $cm^2$) and were at various sites (median femoral condyle 53%, patella 25%, lateral femoral condyle 18%, trochlea 3% and lateral tibial condyle 1%).

### *Intervention*

In the trial by Bentley and colleagues, all patients were randomised after arthroscopy. Residual cartilage was removed from the defect. For the autograft, a 2 × 1 cm full-thickness fragment of articular cartilage was harvested from the edge of the trochlea. Cells were cultured using the patients' serum. Cells were implanted at arthrotomy after 3–5 weeks. In six patients, periostium from the tibia or femur was used to form the flap, and in 46 patients a porcine collagen membrane (chondrogide) was used. The flap was sutured to margins of the defect. Cultured cells (5–10 million cells, mean 5.5) were injected under the flap, before final suture and sealing with fibrin glue.

The comparison group had mosaicplasty, with similar arthroscopy, and débridement of defect as the ACI group. Large mosaic plugs of 4.5 mm in diameter used where possible. They were placed prominently to allow contact with the opposing articular surface during movement. When possible, plugs were taken from the margins of the trochlea. In some patients, plugs were taken from the margins of the intercondylar notch. The slope of the donor articular surface was matched to that to be replaced in the defect. The joint was moved through the full range of movement to check that the mosaics were stable and satisfactorily placed.

Rehabilitation was similar in both groups. A compression Robert Jones type bandage was applied, reinforced by plaster-of-Paris backslab.

The leg was rested and elevated for 12 hours. The patient was encouraged to exercise the foot and ankle and quadriceps using contraction exercises. Movement was not allowed. At 24 hours full weight bearing was encouraged. At 48 hours, a light cylinder cast was applied, with the knee in full extension. Patients were discharged fully weight bearing, but using crutches for support. At 10 days, the plaster was removed, and the patient encouraged to bear weight fully, but using crutches for 6 weeks. Mobilisation was encouraged, with daily physiotherapy for 2 weeks to obtain full range of movement. At about 1 month, other activities were encouraged to obtain maximal mobilisation. Patients were advised to avoid impact loading and twisting. Patients returned to work and normal activities of daily living at variable times between 6 weeks and 6 months, depending on how sedentary their work was. Exercise continued with physiotherapy if required. At 6 months, light jogging was allowed, but no other sporting activity until 12 months post-operatively.

## Results

**Function**

Bentley and colleagues comparing ACI with mosaicplasty, reported no significant difference in the proportion of patients rated as excellent or good on the Cincinnati score at 1 year for all patients combined regardless of defect site [rated excellent or good: 51/58 (88%) with ACI versus 29/42 (69%) with mosaicplasty, $p$ = not significant (ns)]. However, a $\chi^2$ test for trend gives a $p$-value of 0.002, indicating that the ACI group did significantly better (Campbell MJ, Appraisal Committee, October 2004: personal communication). Outcomes were then analysed according to defect site and it was found that ACI significantly increased the proportion of patients whose results were rated as excellent or good on the Cincinnati score at 1 year [excellent or good: 21/24 (88%) with ACI versus 21/29 (74%) with mosaicplasty, $p < 0.05$], for lesions of the medial femoral condyle. The authors report that there was no significant difference between treatments in the proportion rated as excellent or good on the Cincinnati scale at 1 year for patients with either lateral femoral condyle or patellar defects [lateral femoral condyle defects: 12/13 (92%) with ACI versus 2/5 (40%) with mosaicplasty, $p$ = ns; patellar defects: 18/20 (85%) with ACI versus 3/5 (60%) with mosaicplasty, $p$ = ns]. The number of patients in some of these subgroups was very small. There were insufficient numbers of patients with a trochlea or lateral tibial plateau defect for analysis.

**Complications and further surgery**

Bentley and colleagues briefly reported complications, but did not mention any further surgery. A total of three (3%) patients were slow to mobilise and required manipulation under anaesthesia; one of these patients required arthroscopy and arthrolysis to mobilise the knee. One patient developed calf-vein thrombosis and required anticoagulants, and one patient developed a superficial infection which settled rapidly with a course of oral antibiotics for 5 days.

**Histology**

Bentley and colleagues did an arthroscopy on 60 (60%) patients at 1 year after surgery. This represented 64% (37/58) of patients after ACI and 55% (23/42) after mosaicplasty. No details were given of how patients were selected for repeat arthroscopy. A significantly higher proportion of patients undergoing repeat arthroscopy had International Cartilage Repair Society (ICRS) grade 1 or 2 after ACI compared with mosaicplasty [31/37 (82%) with ACI versus 8/23 (34%) after mosaicplasty, $p < 0.01$]. In about 50% of ACI patients the tissue was relatively soft on probing compared with the surrounding cartilage.

Biopsy was not always possible. Nineteen (33%) patients had biopsy after ACI (three from the patella and 16 from the femoral condyle). Seven patients had normal hyaline cartilage (normal structure under polarised light and cells in lacunae, cartilage cells confirmed by the presence of S-100 protein), seven patients had both hyaline cartilage and fibrocartilage, and five patients had fibrocartilage, albeit well bonded to bone. One of the ACI grafts that showed mixed hyaline and fibrocartilage at 1 year had hyaline cartilage alone at the 2-year biopsy. The number of patients having biopsy after mosaicplasty was not stated and results were only reported for seven patients rated poor on the Cincinnati scale. In four patients the plugs were *in situ*, but the tissue between them had not become covered with continuous fibrous tissue, in three patients the plugs had disintegrated, and in one patient the area of the mosaicplasty had remained reasonably intact, but the articular cartilage at the defect margins of the defect had broken down to expose subchondral bone.

Another study from the same centre adds to the information on histology. Briggs and colleagues[66] carried out biopsies in 14 patients 1 year after ACI. Eight patients had hyaline cartilage (six had hyaline only, two had mixed hyaline and fibrocartilage) and the others had fibrocartilage. However, Briggs and colleagues also noted that

even the patients whose biopsies showed fibrocartilage had some type IIa and IIb collagen, suggesting the presence of a mixture of immature and mature chondrocytes. The implication is that further maturation is likely to occur.

In summary, Bentley and colleagues found that ACI gave better results than mosaicplasty at 1 year. Overall, 88% had excellent or good results with ACI versus 69% with mosaicplasty. About half of the biopsies showed hyaline cartilage.

## Horas and colleagues (2003)[65]

### *Description and quality of study*

In the second trial, ACI was compared with the implantation of an autologous osteochondral cylinder in patients with a history of a single traumatic event and a single cartilage lesion in the weight-bearing area of the femoral condyle. Patients were allocated to treatment alternately, which is a design weakness. Inclusion and exclusion criteria were clearly defined. There was no report of an *a priori* sample size calculation. Forty per cent of patients had had previous knee surgery; details were given of the outcome of the initial operation and of any further procedures. Treatment groups appeared similar at baseline with respect to defect size and function assessed using the modified Lysholm score, the Meyers score, and the activity scale described by Tegner and Lysholm. The experience of the surgeons in ACI was not mentioned and it was not stated whether one or more than one surgeon carried out the surgery. It was not reported whether any concomitant surgery was carried out. Rehabilitation programmes were the same for both treatment groups. It was not reported whether the assessor of the clinical outcomes at 1 year was blinded to treatment allocation. The article focused on histological outcomes from a subset of patients who were followed up with repeat arthroscopy and biopsy. Complications and further surgery were reported in detail and by treatment group. The authors declared that they had no potential conflict of interest.

### *Participants*

Horas and colleagues recruited 40 consecutive patients with a history of a single traumatic event, a single cartilage lesion extending to or through the articular cartilage tidemark without an osseous lesion, or a lesion in the weight-bearing area of the femoral condyle, and clinical symptoms such as locking of the joint, pain with weight bearing or squatting, and swelling. Patients were excluded if they had knee joint instability, a matching lesion on the opposing tibial articular surface, axial malalignment, an osteochondral tumour, skeletal immaturity, or degenerative or rheumatoid joint disease. Participants were aged between 18 and 44 years (mean age 33.4 years), 58% were male, weight ranged from 52 to 96 kg (mean weight 75.5 kg) and height ranged from 162 to 192 cm (mean height 177.5 cm). All the cartilage defects were considered to be traumatic in origin, all were full-thickness defects and none involved subchondral bone. Defects ranged in size from 3.2 to 5.6 $cm^2$ (mean 3.75 $cm^2$). Defects were on either the medial femoral condyle (82.5%) or the lateral femoral condyle (17.5%). Forty per cent of the patients had had previous surgery, which included arthroscopy alone (5% of all patients), abrasion (20%), drilling (2.5%), extraction of osteochondral bodies (5%) and incomplete resection of the medial meniscus (7.5%). Some patients had had more than one type of surgery.

### *Intervention*

The depth and extent of the lesion were evaluated at arthroscopy and a slice of healthy cartilage (140–360 g) was removed from the proximal part of the medial femoral condyle. Chondrocytes were isolated using the method of Brittberg and colleagues.[67] After 2–3 weeks of culture, the total cell number was $3.2–6.5 \times 10^6$ chondrocytes in a total volume of 100–160 ml. Exact timing of the implantation of cells was not reported (3–5 weeks?) and cells were implanted through a medial or lateral parapatellar arthrotomy in a tourniquet-controlled, bloodless field. A precisely fitting periosteal flap, from the medial aspect of the proximal part of the tibia, was applied to the defect with the cambium layer facing the subchondral bone. The flap was fixed securely by sutures to the hyaline cartilage. No fibrin glue was used for sealing the defect, and a watertight seal was confirmed using saline. The suspension of cultivated autologous chondrocytes was then injected under the periosteal flap. This was followed by closure of the knee joint.

The comparison intervention was osteochondral cylinder transplantation (OCT) by medial or lateral arthrotomy. The osteochondral transplants were harvested using a diamond bone-cutting system (DECS; Merck, Darmstadt, Hessen, Germany) with a twin pair of carving cylinders differing in diameter by 0.1 mm, which could resurface a cartilaginous area of 0.78 $cm^2$ with the smallest cylinder and an area of 2.26 $cm^2$ with the largest. For defects that required multiple cylinders for joint congruency or for the coverage of large defects, press-fit implantation of several single osteochondral transplants was used.

Post-operative rehabilitation was similar in the two groups. Rehabilitation involved a 4-week protection phase, with no weight bearing during days 1–14, then weight bearing of approximately 9.1–13.6 kg during weeks 3 and 4, and an increase in weight bearing from 25% at 5 weeks to full at 12 weeks. Range of motion was limited to as little as 0 degrees to as much as 90 degrees for the first to tenth days, increased by 5–10 degrees per day for the 11th to 21st days, and was limited to as little as 0 degrees to as much as 130 degrees from the fourth to 12th weeks. After 12 weeks, a free range of movement was permitted. During weeks 1–4, active and passive physiotherapy was begun immediately. This included patellar mobilisation, stretching of the hamstring, calf and quadriceps muscles, straight-leg raises and CPM. From 4 weeks the programme continued with isometric leg-press exercises, proprioceptive neuromuscular facilitation and aqua-jogging. At 5–6 weeks (transition period) this was followed by mini-squats (with 0–45 degrees of knee flexion), and closed and open-chain kinetic exercises were initiated, and the patient progressed with weight-bearing from 8–9 weeks post-operatively. At 7–12 weeks (maturation period), bilateral squats (0–60 degrees), leg-press exercises (0–90 degrees), a walking programme, swimming, and the use of a Stairmaster were included. After 12 weeks, patients were generally allowed full activity. They were advised to refrain permanently from participation in competitive contact sports such as soccer, basketball and hockey. A brace was not used in either treatment group.

### *Results*

#### Function

Horas and colleagues assessed outcomes at 3, 6, 12 and 24 months using three clinical measures: the modified Lysholm score, the Meyers score, and the activity scale described by Tegner and Lysholm. They found that patients improved with both treatments. Patients allocated to ACI had significantly lower (poorer) Lysholm scores at 6, 12 and 24 months than patients allocated to OCT [Lysholm score (best = 100, worst = 0), 6 months: 45.75 with ACI versus 53.45 with OCT; 12 months: 57.50 with ACI versus 68.25 with OCT; 24 months: 66.75 with ACI versus 72.70 with OCT, $p < 0.05$ for all periods]. The trial found no significant difference between ACI and OCT for any time period when patients were assessed using the Meyers score or the Tegner score (Meyers score: 7.20 at baseline to 15.95 at 24 months with ACI versus 7.85 at baseline to 16.75 at 24 months with OCT; Tegner score: 1.60 to 5.10 with ACI versus 1.60 to 5.20 with OCT, $p$ not reported).

#### Complications and further surgery

Horas and colleagues reported a similar proportion of patients with complications within 24 months after ACI and after OCT [12/20 (60%) with ACI versus 12/20 (60%) with OCT]. Seven patients had complications after ACI that required further surgery. These included occasional locking of the joint and adhesions, anterior cruciate ligament partial rupture post-ACI, extension deficit, concretion of the knee capsule, functional malalignment, lateralisation of the patella and recurrent knee joint effusion plus extension deficit. Five patients had complications after ACI that did not require further surgery. These included recurrent knee joint effusion plus extension deficit, recurrent knee joint effusion, passing irritation of the infrapatellar branch of the saphenous nerve and swelling of the knee joint. In addition, one patient reported as having no complications after ACI had an arthroscopy 24 months post-ACI in case of meniscopathy. Seven patients had complications after OCT that required further surgery. These included extension deficit, post-operative haemarthrosis, multiple joint effusions for 8 weeks plus flexion joint deficit, occasional locking of the joint during flexion plus adhesions in the medial recessus, and flexion deficit plus adhesions in the cranial recessus. Five patients had complications after OCT that did not require further surgery. These included two patients with flexion deficits, superficial wound infection plus flexion deficit, passing irritation branch of the peroneal nerve and passing irritation infrapatellar branch of the saphenous nerve. In addition, two patients reported as having no complications after OCT had further surgery (arthroscopy due to new cartilage lesion after knee distortion plus spongiolisation and arthroscopy 3 months post-OCT due to screw revision plus spongiolisation).

#### Histology

Horas and colleagues performed eight biopsies in six patients (30% of total) within 24 months of undergoing ACI and biopsied five patients (25%) at 3–22 months following OCT. No details were reported of how patients were selected for biopsy. In the ACI group, eight biopsies from six patients showed on scanning electron microscopy that the regenerated tissue had characteristics of fibrocartilage plus empty chondrocyte-sized holes in central and deeper layers. The regenerated tissue had a rigid, elastic consistency and a rippled surface; in five of the eight cases, there was a distinct, rough surface. In two patients, the regenerated tissue had overgrown the level of the surrounding cartilage. Staining for type I collagen

was multifocally positive in the regenerated tissue and negative in the adjoining original cartilage. Conversely, staining for type II collagen was distinctly positive in the original cartilage and only focally verifiable in the regenerated tissue, where it was essentially limited to the deep layers. Scanning electron microscopy at 24 months showed regenerated tissue that was tightly united with the original cartilage.

In the OCT group, three patients were assessed at 3 months and two at 21 or 22 months. Biopsies were taken from the interface between resident cartilage and transplant. All showed macroscopically vital cartilage with a persistent, almost circular, gap at the level of the cartilage, but seamless integration in the osseous layer. There was no obvious difference between the transplanted and surrounding resident cartilage macroscopically, and the consistency was the same. There were no clinical signs of degeneration of the articular cartilage. The surface was smooth and appeared adapted to the natural convexity of knee joint. The donor areas were filled with fibrous-appearing tissue. Cartilage–bone cylinders taken from the interface showed unreactive hyaline cartilage transplant adjacent to the resident hyaline cartilage with haematoxylin and eosin staining, and a gap reaching down to the bone. Immunohistochemical staining for collagen types II and IV and protein S-100 was characteristic of hyaline cartilage in the five samples. Scanning electron microscopy revealed that the transplant had maintained its original tidemark and did not appear different from the surrounding cartilage in either the deep or the superficial layer.

In summary, Horas and colleagues found little difference in clinical outcomes at 2 years. Disappointingly, biopsies from the ACI group showed fibrocartilage rather than hyaline cartilage.

## Knutsen and colleagues (2004)[63]

### *Description and quality of study*

The third RCT (80 patients) compared ACI with microfracture for the repair of isolated articular defects on the medial or lateral femoral condyle and assessed outcomes at 24 months using the Lysholm score, a visual analogue scale (VAS) pain score and SF-36 for assessment of quality of life. Eligible patients were randomised during arthroscopy using sealed envelopes. Power calculation found that a sample size of 40 patients in each group was required to have a 90% probability of detecting a difference of at least 0.75 SD from the mean for Lysholm or SF-36 scores with $\alpha$ of 0.05. Most patients (94%) had had previous knee surgery and details were given of the type of operation, but no information was given on the outcomes of these previous operations. Treatment groups were similar at baseline with respect to age, gender, defect size, body weight and baseline clinical data. It was stated that surgeons were well trained in both surgical techniques, but the number of surgeons carrying out the operations was not reported. Rehabilitation programmes were the same for both treatment groups. The assessor of outcomes was blinded to treatment group. Patients who experienced a treatment failure were reported as having been "excluded from the study", implying that analysis was not on an ITT basis, but the number of patients analysed was not specifically stated. Some adverse effects were reported by treatment group, but it was not clear how comprehensive the reporting of adverse effects was. The authors of the trial stated that they had no potential conflict of interest.

### *Participants*

Knutsen and colleagues recruited 80 patients with an isolated symptomatic defect on medial or lateral femoral condyle in a stable knee and with normal standing radiographs. Patients had to have symptoms (pain, catching, locking or swelling with reduction in activities) that were considered likely to be related to the cartilage defect. Patients were excluded if they had misused alcohol or drugs in previous 3 years, if they had osteoarthritis/rheumatoid arthritis, gout, Bechterew syndrome or chondrocalcinosis, malalignment with more than 5 degrees of valgus or varus compared to normal, were overweight [body mass index (BMI) > 30] or had any serious illness. The mean age of patients was 32.3 years, 60% were male and the median duration of symptoms was 36 months. Most defects were traumatic (65%) in origin, with another 28% due to OCD. Defects were located predominantly on the medial femoral condyle (89%), with 11% located on the lateral femoral condyle. The mean defect size was 4.8 $cm^2$. Most (94%) patients had had previous surgery, including arthroscopic lavage and débridement (36%), anterior cruciate ligament reconstruction (19%), meniscal surgery (18%), Pridie drilling (4%), and operations for OCD such as drilling or fixation of a fragment (16%).

### *Intervention*

The method described by Brittberg and colleagues[67] was used for chondrocyte implantation. Cartilage was harvested

arthroscopically from the low load-bearing area on the proximal part of the medial femoral condyle of the affected knee. Cells were cultured in the Genzyme laboratory in a sterile transport medium provided by Genzyme for approximately 4 weeks. Cells were implanted at arthrotomy after about 4 weeks after débridement to healthy surrounding cartilage. As a flap, periostium from the proximal tibia or distal femur was used and the flap was sutured to the rim of debrided defect, which was sealed with fibrin glue after injection of the cultured cells under the flap.

Microfracture was used as the comparison intervention and was done at the same time as initial arthroscopy using the technique described by Steadman[40] after accurate débridement of all unstable and damaged cartilage including the calcified layer down to subchondral bone. All loose or marginally attached cartilage was debrided from the surrounding rim of the defect to give a stable perpendicular edge of healthy cartilage. An arthroscopic awl used to make multiple holes in the defect, 3–4 mm apart.

Post-operative rehabilitation was the same for both interventions. All patients were hospitalised for 4 days. CPM and partial weight bearing with crutches began on day 1. During the first 8 weeks, partial weight bearing (20 kg) with crutches was allowed, and full weight bearing depending on clinical status and function at 8–12 weeks. Stationary cycling started as soon as possible.

## Results

### *Function*

The study assessed the following clinical outcomes at 12 and 24 months: the Lysholm score, pain on a 0–100 VAS, quality of life using SF-36 and treatment failure (defined as requiring a reoperation because of symptoms due to lack of healing of the primary treated defect; the need for shaving or trimming a lesion was not defined as failure). The study found that both types of surgery significantly improved Lysholm scores and reduced pain from baseline at 1 to 2 years (Lysholm score: $p < 0.005$ for ACI and $p < 0.0001$ for microfracture; pain: $p < 0.0001$ for both). It found no significant difference between treatments at 1 or 2 years using either Lysholm scores or pain. After 2 years, 78% of patients who had had ACI had less pain compared with 75% after microfracture. Microfracture significantly improved SF-36 quality of life scores compared with ACI at 2 years ($p < 0.005$), but patients who had microfracture had lower scores at baseline. These scores have to be taken from graphs, since no table of baseline status is given. The baseline scores for the Lysholm and VAS pain scores are similar, so it is puzzling that there was so much difference in the SF-36 scores. After adjusting for pre-operative scores (method not given), microfracture still significantly improved SF-36 physical component scores compared with ACI ($p = 0.01$). There was no significant difference between treatments in the mental health subscale. Subgroup analyses found that patients under 30 years of age had significantly better clinical outcomes with both treatments than older patients ($p = <0.01$), but the age distributions of the two groups are not given. More active patients had significantly improved Lysholm scores, less pain and better SF-36 physical component scores with both treatments than less active patients ($p = 0.0005$). Patients with smaller lesions (<1 cm) who had undergone microfracture had significantly improved Lysholm scores, less pain and better SF-36 physical component scores than patients with larger defects ($p < 0.005$). This association was not found with ACI.

**Complications and further surgery**

Few patients were classified as treatment failures [ACI: 2/40 (5%) at 6 and 18 months compared with microfracture: 1/40 (2.5%) at 15 months]. All patients classified as treatment failures were symptomatic and underwent revision with another cartilage treatment. Patients who consented had a second look arthroscopy and biopsy (where possible) at 2 years (ACI: 32 patients, microfracture: 35 patients). Arthroscopic débridement was performed in ten (25%) ACI and four (10%) microfracture patients. In ACI patients, shaving was done mainly because of symptomatic tissue hypertrophy. Among microfracture patients, one patient had adhesions (needed manipulation and operative release) and three patients had minor débridement.

**Histology**

Knutsen and colleagues performed second look arthroscopy 2 years after surgery in 67 (84%) patients. Biopsy was performed in 32 out of 40 (80%) after ACI and 35 out of 40 (88%) after microfracture (others refused repeat arthroscopy or were pregnant, or suitable biopsies were not obtained). There was no significant difference between ACI and microfracture in mean ICRS score. Overall, some hyaline was present in 39% of biopsies, but few were composed totally of hyaline. Fibrocartilage was present throughout most of the depth in 43% of specimens. There was no significant difference between ACI and microfracture in the frequency of hyaline and

fibrocartilage repair tissue, but the number of specimens may not have been sufficiently large to detect a significant difference (120 biopsies would have been necessary to find a significant difference between groups). Findings were graded as nearly normal in both groups. The trial found no association between clinical outcome according to the Lysholm score, pain and quality of life (SF-36) and histological quality according to semiquantitative grading of specimens as group 1, 2, 3 or 4.

In summary, Knutsen and colleagues found only small differences in outcomes at 2 years between ACI and microfracture.

### Basad and colleagues (2004)[62]

#### *Description and quality of study*

The fourth RCT compared MACI with microfracture for post-traumatic, single, symptomatic and isolated chondral defects of the femoral condyle or patella. Outcomes were assessed using the Meyers score, the Tegner–Lysholm score, the Lysholm–Gillquist score, the ICRS classification and MRI. Forty-six patients were included, but outcomes were only reported for 19 at 1 year and five at 2 years. Details regarding randomisation, power calculation, previous surgery, experience of the surgeon and blinding were not reported. Details regarding similarity of the groups at baseline were not reported, although a table showing International Knee Documentation Committee (IKDC) scores at baseline suggests that the two groups were not equivalent (but no statistical analysis is given). Details of post-operative rehabilitation were not given and treatment failures and other adverse effects were not reported. Details about conflict of interest were not stated.

#### *Participants*

The trial included 46 patients, but 1-year results were available for only 19 and 2-year results for only five patients. Inclusion criteria were not clearly stated, but patients had post-traumatic, single, symptomatic (not defined) and isolated chondral defects of the femoral condyle or patella. Exclusion criteria were not stated. The mean age of patients was 33 years; gender was not stated, nor was the aetiology of the lesion. Defect size was between 2 and 10 $cm^2$.

#### *Intervention*

Basad and colleagues used MACI. A cartilage biopsy was obtained during initial arthroscopy, and a collagen type I/III membrane was loaded with the cells 3–4 days before implantation; the matrix was fixed into the chondral defect using fibrin glue during the second surgical intervention (by miniarthrotomy). No details were given regarding harvesting of chondrocytes. No flap was used.

The comparison intervention was microfracture, done in a single arthroscopic procedure. No details were given regarding rehabilitation.

#### *Results*

**Function**

No significance values were reported. At 1 year, the Meyers score was improved by +6.5 in the MACI group and by +1.9 in the microfracture group, the Lysholm–Gillquist score was improved by +27.4 in the MACI versus +4.1 in the microfracture group, the Tegner–Lysholm score was improved by +32.6 in the MACI versus +15.3 in the microfracture group, and ICRS classification improved in both groups but with no differences between groups.

**Complications and further surgery**

The study by Basad and colleagues did not report treatment failures or complications.

**Histology**

Basad and colleagues performed MRI; during the first 12 months no complete equalisation of MRI signal intensity to surrounding tissue was achieved in the MACI group, but this was achieved at 24 months, with the thickness of regenerated tissue being 1–1.8 mm (implanted graft was 0.5 mm). In the microfracture group, partially different signal intensities compared with normal surrounding cartilage were obtained.

In summary, there are too few long-term results at present, but the study does show the feasibility of doing ACI by the MACI technique. It also shows that after ACI, it takes 2 years for full-thickness cartilage to be produced.

## Other studies

### Randomised trials comparing different forms of ACI

Two trials were identified comparing different forms of ACI. The Stanmore UK Multi-centre study (confidential submission from RNOH) compares ACI with MACI, whereas the study by Schneider and Andreya[58] compares standard ACI with CaReS (here, chondrocytes are grown directly in a collagen gel).

*[Confidential material removed]*

The study by Schneider and Andreya[58] showed no difference between the ACI group and the CaReS group in terms of IKDC scores (20 patients with femoral or retropatellar defects). Again, no details are available on operative technique, but the authors report that operation times were significantly shorter in the CaReS group (69 minutes versus 107 minutes in the standard ACI group). The authors also argue that traditional cultivation of cells may lead to dedifferentiation of cells (with an unknown effect on clinical outcomes), and this dedifferentiation may be minimised by growing cells in a three-dimensional system as used in CaReS.

## Long-term results from case series

### ACI

In three reports, Peterson and colleagues[68–70] describe outcomes for patients who had ACI with up to 11 years' follow-up. Participant numbers ranged between 58 and 101, and ACI was performed for moderate to large full-thickness chondral defects of the knee and OCD. Good or excellent results were observed in between 82 and 92% of patients. In one study, adverse events occurred in over 50% of participants (three superficial wound infections, one post-operative fever, two post-operative haematomas, ten intraarticular adhesions, 26 periosteal hypertrophies and seven graft failures), in the other two studies graft failures occurred in 16% and 3% of participants.

This study is useful for showing that after both interventions, benefit is sustained for up to 11 years. If benefit was a gain in quality-adjusted life-years (QALYs) of 0.1, this would equate to 1.0 QALY over 10 years.

### Natural history

Prakash and Learmonth[18] studied the natural progression of isolated osteochondral defects in the femoral condyle in 15 knees (12 patients) over an average of 109 months (minimum follow-up 4 years). Patients were selected from old theatre records (arthroscopy patients) and from MRI scan records. Age was between 9 and 49 years and follow-up between 54 and 282 months. Patients were assessed using the Lysholm score and MRI scans. At follow-up, children (below 18 years) had a higher Lysholm score than adults (77.1 for children versus 49.9 for adults), although the Mann–Whitney test was inconclusive. MRI scans showed that in six out of seven children the lesion had healed, but only in two out of eight adults, with the remaining six showing signs of osteoarthritis.

Messner and Maletius[17] followed up 28 young athletes (ages 14–38, mean 25 years) who had no surgical treatment. All had severe (grade 2 or 3) chondral damage with minimum diameter 1 cm. The median duration of symptoms at baseline was 12 months. Fourteen years later, despite lack of treatment, ten had excellent function, 12 had good function and six had problems. Symptoms such as pain and locking had resolved in most cases, but most noticed some pain on strenuous exercise. Furthermore, X-rays showed loss of joint space in 16 of the 28 knees. So, while clinical outcomes were good, the loss of joint space suggests that osteoarthritis is developing, and that the longer term outcomes will not be so good.

There is one very interesting result from this study. Messner and Maletius X-rayed both knees. The originally unaffected knees showed less early osteoarthritis than the knees with the known lesions, but ten out of 28 showed radiographic evidence of osteoarthritis. Hence, in radiographic terms, there was no significant difference between the originally injured and uninjured knees. One possibility is that the group of people who sustain these sporting injuries are going to wear out both knees; if so, ACI or any other intervention would not have a long-term effect in avoiding osteoarthritis and future knee replacements.

Shelbourne and colleagues[19] studied a group of patients who had had cruciate ligament surgery, during which chondral defects were seen but not treated. They were followed up and compared with a control group from the cruciate series who had not had a chondral defect. The authors report that there was little difference in clinical (Noyes) scores at a mean of 8.7 years: the scores were all very good. Fifty-two of the chondral lesions patients were X-rayed at a mean of 6.3 years; they showed no significant difference from the X-ray findings in the uninjured group. The usual caveat applies: 6 years is a short time in the life of a knee.

### Microfracture

Blevins and colleagues[71] studied 38 high-level and 140 recreational athletes (aged 13–68 years, 76–77% male) for an average of 3.7±1.4 years. Of 31 high-level athletes assessed, 77% returned to competition and 71% reported function to be equal or superior to preinjury level. Complications

were not systematically reported, but no reflex sympathetic dystrophy was seen, and occasional patients reported localised pain. Steadman and colleagues[72] studied 75 knees with full-thickness traumatic defects in 72 patients (aged 13–45 years, 66% male) after 7–17 years of microfracture. At final follow-up, 23 knees were pain free, 38 had mild pain and ten had moderate pain. Eighty per cent of patients rated themselves as 'improved'. The authors report that there were no peri-operative complications.

### Mosaicplasty

Hangody and Füles[73] studied 652 mosaicplasties, 578 of which were done on the knee (461 femoral condyles, 93 patellofemoral joints and 24 tibial plateaux). Two-thirds (of all 652 patients studied) had a grade III or IV cartilage lesion and one-third had an osteochondral defect. In 86% of patients concomitant surgical procedures were carried out (mainly anterior cruciate ligament reconstruction, realignment osteotomies, meniscus surgery and patellofemoral alignment procedures). Other patient characteristics were not described. Implantations were evaluated using the modified Hospital for Special Surgery, modified Cincinnati, Lysholm and ICRS scoring systems. Good or excellent results were obtained in 92% of patients with femoral condylar implantations, in 88% of patients with tibial resurfacing, and in 81% of patients with patellar mosaicplasties, trochlear mosaicplasties or both. Fifty-eight out of 68 control arthroscopies showed good gliding surfaces, histologically proven survival of transplanted hyaline cartilage and fibrocartilage covering donor sites. Complications were seen in 40 cases (four deep infections, 34 painful haemarthroses and three thromboembolisms).

## Issues with evidence for clinical effectiveness

The technology is still evolving, and new studies of newer methods of culturing the cells in a collagen matrix, or seeding them on to membranes, are underway. Periosteal capping is being replaced by the use of collagen I/III membranes.[74] Since periosteal caps were prone to hypertrophy requiring shaving, that may reduce the need for subsequent operations. In a series of 135 patients from Melbourne treated with ACI, 22 required further surgery, in most cases due to problems with the periosteal cap.[75] Since the intention is always the same – to repair the damaged area with hyaline cartilage – the end result may be the same, but costs may differ.

In the short term (2–10 years), most patients do well with most treatments, and even with natural history. In the longer term, there is a general consensus that filling defects with high-quality hyaline cartilage will provide lasting benefit, but that fibrocartilage will eventually crumble, leading to osteoarthritis. However, neither the trials nor the case series provide data on how long fibrocartilage will last before knee replacement becomes necessary, or in what proportion of patients TKA will be needed. In Steadman's series after microfracture, many of those classed as failures decide not to have further surgery. Nor is there any very long-term evidence on how long hyaline cartilage produced by ACI will last; it may be less durable than the original. Another problem is mixed fibrocartilage and hyaline cartilage: will mixed last longer than fibrocartilage? None of the studies is yet long enough to provide data on the key outcome: avoidance of osteoarthritis and knee replacements.

Different trials give different results for the proportion who get hyaline after ACI, with higher proportions in the trial by Bentley and colleagues[64] and in the case series reported by Henderson and colleagues[75] than in the trial by Horas and colleagues.[65]

If one assumes that hyaline cartilage is the desired outcome, on the basis that hyaline cartilage can last for life (most people do not need knee replacements in their lifetime), then ACI becomes the best option (in clinical effectiveness terms) because it gives the highest chance of the defect being filled with hyaline cartilage. All other options will at best provide mixed cartilage. Mosaicplasty will have plugs of hyaline surrounded by fibrocartilage. However, in the ACI studies, many patients did not achieve hyalinisation.

Knee replacement is currently considered undesirable in people aged under 55 years, partly because of the fear that the replacement will need to be replaced. However, future knee prostheses may last longer, and hence TKA may be done at younger ages. The people for whom ACI or alternatives were being considered in 2004 would be unlikely to need TKA before 2020, by which time knee prostheses may have improved.

# Chapter 4

# Cost-effectiveness

This chapter starts by reviewing the existing economic literature on ACI, including some unpublished or commercial in confidence data (removed from this version) from submissions to NICE. Some economic analyses are then carried out. Because of data deficiencies, these are illustrative rather than definitive.

## Previous economic studies of ACI

The economic studies of ACI, microfracture and mosaicplasty can be grouped by:

- costing studies
- quality of life studies
- cost–utility studies.

These classifications are used to summarise the papers arising from the economic literature search and the economic aspects of the industry submissions.

The submission from TeTec briefly summarises the conclusions of the Lindahl,[76] Minas[77] and Wildner[78] papers. This is not repeated, and nothing further has been drawn from the TeTec submission as regards economics. No submission has been received from Genzyme.

### Costing studies

Lindahl and colleagues,[76] in a case-series study of 57 Swedish patients undergoing ACI, compared the 10-year cost pre- and post-ACI. Pre-operative clinical status was assessed through a retrospective evaluation of medical records and questionnaires. The patient group was split by location between those for whom a minimum of 5-year follow-up data were available and those for whom a minimum of 2-year follow-up data were available.

Before ACI the average 10-year surgical cost was SEK41,137 (1998 SEK costs, discount rate of 3% applied) (£3557) for arthroscopy and rehabilitation (2003 prices converted at prevailing exchange rates of 13.3SEK/£ and inflated at Hospital and Community Health Services (HCHS) inflation: approximately 15% for this period). ACI surgery and rehabilitation were costed at SEK181,377 (£13,637). Additional arthroscopic and rehabilitation costs of SEK6170 (£533) during the following 10 years are cited, although this appears to rely on an assumption of an average of 0.25 further operative procedures post-ACI:

- 10-year pre-ACI medical costs: SEK41,137 (£3557)
- 10-year post-ACI plus ACI medical costs: SEK14,492 (£1253)
- 10-year pre-ACI absenteeism costs: SEK859,898 (£74,352)
- 10-year post-ACI absenteeism costs: SEK181,377 (£15,683).

The cost break-even point for further operations post-ACI is given as around 1.75, but this includes the costs of absenteeism and is of limited relevance to the NICE reference case. The base case suggests that ACI is cost-saving relative to débridement over a 10-year period.

Wildner and colleagues[78] develop a deterministic Markov model of the cost-effectiveness of ACI relative to mosaicplasty and microfracture, the outcome being years free of knee replacement. Overall treatment costs amount to DM21,000 (£8242) for ACI, DM5400 (£2119) for microfracture, and DM6000 (£2354) for mosaicplasty, these costs being the costs to the health system and health insurance system in Germany (prices converted as for SEK/£, but at a rate of DM2.95/£). Using a discount rate of 3% for both financial and health effects, the overall treatment costs and prosthesis-free life years are:

- DM13,657 (£5360) and 22.6 years for microfracture: ICER=DM630 (£247)
- DM 14,257 (£5595) and 22.6 years for mosaicplasty: dominated
- DM25,128 (£9862) and 23.9 years for ACI: ICER=DM9032 (£3544)

Mosaicplasty remains dominated with a 0% discount rate.

*[Confidential material removed]*

### Quality of life studies

The only study of long-term quality of life among patients receiving any of the treatments under

***TABLE 2*** *Quality of life and clinical status measurements before and after procedures*

| | Pre-operative | | 12 months | | 24 months | |
|---|---|---|---|---|---|---|
| | **ACI** | **Microfracture** | **ACI** | **Microfracture** | **ACI** | **Microfracture** |
| SF-36 physical component | 41 ± 1.5 | 37.5 ± 1.5 | 42.5 ± 2 | 43 ± 2 | 42 ± 2 | 46 ± 2 |
| SF-36 mental component | No significant difference between the two groups | | | | | |
| VAS pain score | 54 ± 5 | 53 ± 3 | 41 ± 6 | 35 ± 6 | 35 ± 5 | 32 ± 5 |
| Lysholm | 58 ± 4 | 56 ± 3 | 69 ± 6 | 78 ± 3 | 71 ± 4 | 76 ± 4 |
| Data are taken from graphs. | | | | | | |

consideration is by Steadman and colleagues.[72] This examines the effectiveness of microfracture among 72 patients, with an average 11-year follow-up. Unfortunately, given the length of the study, SF-36 was only available and administered towards its end. Statistically significant improvements were noted in Lysholm scores. Reductions in pain and swelling were largely experienced in the first 2 years, these reductions being maintained over a 7-year period. Activity levels among microfracture patients similarly improved over 2 years, these gains being maintained over 7 years.

Knutsen and colleagues[63] in an RCT, allocated 80 patients equally between ACI and microfracture, assessing quality of life and clinical status pre-operatively, at 12 months and at 24 months. Both groups showed significant clinical improvements over the 2 years, but no statistically significant differences in either the VAS pain score or the Lysholm score were seen between the two groups (*Table 2*). The SF-36 physical component was the only dimension noted as having a statistically significant difference between the two groups, with the improvement in the microfracture group being significantly larger than that for the ACI group. Even controlling for the lower pre-operative value for the physical component in the microfracture group, the microfracture group physical component score remained statistically significantly greater. Regardless of treatment, greater effect was seen among younger patients.

Minas,[77] in a case series, assessed 44 ACI patients pre-operatively and at 12 and 24 months' follow-up:

- SF-36 physical component 33.32, pre-operatively 41.48 at 12 months, this gain being maintained at 24 months
- SF-36 mental component 49.32, pre-operatively 51.56 at 12 months
- SF-36 social functioning 57.10, pre-operatively 81.25 at 12 months.

Of the rest of the eight SF-36 dimensions, physical functioning, role–physical, bodily pain, vitality and social functioning showed statistically significant improvements, although the values for these are not given. Minas then produces a cost per QALY, but does not explain how the SF-36 results are converted to a utility QALY gain, nor does he give a figure for the QALY gain. In correspondence following a comment on the original paper, Minas[79] states that the quality of life increment from these changes amounts to 0.10675. The derivation of this figure is unclear, but implies that there is a reasonable gain to patient quality of life [Quality of life (QoL) is measured over the range 0.0–1.0, 0.0 being death, 1.0 being perfect health. If a patient were to have a pre-operative QoL of 0.6, the QoL improvement of around 0.1 would take the patient's post-operative QoL to 0.7. If this QoL gain were maintained over 1 year, the patient would have gained 0.1 QALYs. If the QoL gain persisted for 2 years, the patient would have gained 0.2 QALYs.]

Minas and Marchie[80] administered the SF-36 to 148 ACI patients at baseline, and 6, 12 and 24 months' follow-up to assess the prognostic value of the SF-36. The average improvement in physical functioning was 20.15. The vitality score and the social functioning score at baseline were particularly positively associated with the improvement in physical functioning.

The West Midlands Development and Evaluation Report by Jobanputra and colleagues[81] conducted a mapping exercise between EuroQol 5 Dimensions (EQ-5D) and quality of life based on expert clinical opinion, to inform their own model development. This suggested a quality of life improvement from 0.689 pre-operatively to 0.796

following successful ACI. Expert clinical opinion could not distinguish this quality of life improvement from that of other surgical treatments such as microfracture, and the same values were used for successful outcomes.

*[Confidential material removed]*

*[Confidential material removed]*

EQ-5D can be criticised as being a relatively blunt generic instrument for collecting health status data, in that its five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) can only be rated as 'no problem', 'some problem' or 'major problem'. The results of Dolan,[82] with an adjusted $R^2$ of 0.46, show that moving from 'no problem' to 'some problem' in any of the dimensions reduces utility, as would be expected, but that this reduction is much greater, typically a three-fold difference, if any 'major problem' is recorded. In addition to these reductions, if any dimension is rated as a 'major problem', the utility score is reduced by a further 0.27. (Note that Dolan[82] provides only the central parameter estimates. This may be of concern given the low explanatory power of his model.)

It may not be unreasonable to characterise the EQ-5D social tariffs in the first instance as being dichotomous between 'no major problem' and 'major problem' within the five dimensions. Any distinctions between 'no problem' and 'some problem' are likely to be of a distinctly second order of importance. In a small sample it would only require a few patients to record a 'major problem' in one dimension potentially to have a major impact on the sample's average utility level.

The RNOH submission includes the abstract of the Bartlett[83] paper. This case series examines the role of SF-36 in the pre-operative and post-operative evaluation of patients undergoing ACI, comparing this with the Modified Cincinnati Knee Score.

SF-36 was administered to 25 patients pre-operatively and at follow-up at 12 months. Before surgery all patients scored lower for all aspects of general health and functioning. At 12 months significant improvements were seen in:

- physical functioning, going from 44.8 to 56.2 ($p = 0.014$)
- role–physical, going from 35.0 to 52.2 ($p = 0.044$)
- bodily pain, going from 33.6 to 50.9 ($p = 0.001$).

Higher pre-operative SF-36 scores were found to correlate with a greater improvement in the Cincinnati Knee Score, but the Cincinnati Knee Score correlated poorly with some aspects of SF-36 (the vitality, social functioning and emotional domains), capturing only a limited amount of the patient health impact. Again, this study shows that ACI is of benefit, but does not help in assessing the benefit, and hence cost-effectiveness, relative to comparators.

The British Society of Rheumatology (BSR) submission summarises some results from the Pavesio[84] paper. This summary appears to indicate a case-series study of 175 ACI patients. EQ-5D was administered apparently pre-operatively and at follow-up at 20 months, although it is unclear to how many patients it was administered. Health gains were seen in 83.3% of patients under EQ-5D, statistically significant improvements ($p < 0.0001$) being recorded in pain and mobility. Subjective improvements in knee function were reported by 92% of patients through the IKDC subjective knee evaluation form. Among 76 patients examined under the IKDC objective knee examination, 88.2% were judged to have normal or nearly normal knee function. A 4.6% complication rate and 1.7% failure rate were noted.

## Cost–utility studies

Minas[77] assumes that the quality of life gain of 0.10675 from ACI will be maintained for 40 years, without explaining how this figure was derived. This gives an overall gain of 4.27 QALYs (undiscounted), which when combined with a cost of $29,000 (£20,460) for ACI gives a cost-effectiveness ratio of $6791 (£4791) per QALY (currency and inflation conversion as before, but at a prevailing rate of $1.63/£). Sensitivity analyses as to the effects of age show cost-effectiveness to increase linearly as age is reduced, owing to the assumption of quality of life gains being maintained to 80 years of age and no discounting being applied.

There are two other problems with this study. First, it lacks a control group, and in effect assumes that the patients would have had no improvement if left untreated. Natural history studies report recovery. Second, it is not known how well these patients would have fared with other options such as microfracture.

*[Confidential material removed]*

## Analysis of cost-effectiveness

The potential impacts of ACI, microfracture and mosaicplasty range from the short-term benefits from symptom relief, restoration of activities and consequent quality of life improvements, through to the maintenance or otherwise of these quality of life benefits in the medium term, and on to the possible impact on the development of osteoarthrosis, and the need for primary and secondary knee replacements in the long term.

Ideally, evidence would be available as follows:

- RCTs of the different interventions, against each other to give relative benefits, and against natural history to give absolute benefits; although if only one, say microfracture, had been assessed against natural history, and then the others had been trialled against microfracture, that would have sufficed
- short-term and long-term benefits, including data on decline in quality of life due to increasing osteoarthritis in the years preceding knee replacement in those whose interventions are not successful
- accurate costs over a 20–30-year period.

Evidence from the RCTs, case studies and expert opinion[63,77,80,81] on quality of life values measured through generic instruments such as EQ-5D and SF-36 is limited to around 2 years. Follow-up studies that give success rates from disease-specific ratings and/or patient self-assessment of improvement are available with around a 10-year time horizon for both ACI and microfracture,[68–70,72] but for only around 4 years for mosaicplasty.[73] However, these are case series from centres of excellence, each specialising in one operation, and one cannot tell how well each group would have done had they had one of the other procedures. No long term studies are available as regards clinical outcome, the incidence of osteoarthritis within the patient population and the need for total knee replacement (TKR). In the life of a knee, 'long term' means 20–30 years or more.

It is therefore not possible to produce an accurate cost per QALY for ACI relative to comparators, because the data required are not available.

Given that, the only options are to abandon estimation of the cost per QALY, or to carry out some illustrative modelling to show what might be concluded from existing data, or from some assumptions where data are absent. Some assumptions are made that seem reasonable, but there is no evidence to support them. If there was, there would be no need to be making assumptions. Please note that what follows is what **might** happen **if** these assumptions were true.

Therefore, some modelling is provided of the cost-effectiveness of ACI in three, increasingly speculative stages:

- short term: the application of the quality of life improvements at 2 years coupled with the immediate treatment costs, and a projection of these quality of life gains forward to 10 years
- medium term: as for the above, only modified by the 10-year success rates reported in the case series
- long term: modelling of the long-term effectiveness of treatment with an assumption such as only hyaline cartilage development prevents osteoarthritis and the need to offer TKR to some or all patients.

### Short-term modelling

The starting point for all modelling is patients who have received a diagnosis and initial washout and débridement. As these initial costs are common to all patients, they have not been included in the modelling. Treatment costs are taken from Aberdeen Royal Infirmary (ARI), including the costs of surgery, days as an inpatient and follow-up physiotherapy (*Table 3*). The costs of cell culture in ACI are taken from the Verigen submission.

Different treatments may have different complication rates, which will lead to additional costs. The literature shows widely differing complication rates among studies, but the within-study differences in complication rates between treatments appears less varied. In the absence of firm data as to the complication rates of the treatments under consideration, these have been taken to be the same and assumed to net out. This will overstate the cost-effectiveness of moving from washout, débridement and no further treatment to any of the three operations, but the main uncertainty is the cost-effectiveness of moving between surgical treatments. This will not be affected by ignoring the complications rate, provided that these are relatively similar between surgical treatments.

Neither the literature nor the industry submissions have shown a clear difference in the quality of life gain from one surgical treatment compared with that from another.

***TABLE 3*** *Resource usage (ARI)*

| | Length of stay (days) | Theatre time (minutes) | Physiotherapy | Procedure cost | Cell culture cost |
|---|---|---|---|---|---|
| Arthroscopy (day case) | 0 | 20 | Nil | £552 | |
| Mosaicplasty | 2.5 | 120 | 15–20 sessions | £3,710 | |
| Microfracture | 2 | 60 | 15–20 sessions | £2,348 | |
| ACI arthroscopic | 1.5 | 90 | 2 IP and 10 OP | £3,184 | £3,200 |
| ACI open knee | 7.5 | 90 | 8 IP and 10 OP | £5,446 | £3,200 |
| First knee replacement | 6 | 150 | 6 IP and 3 OP | £5,417 | |
| Second knee replacement | 12 | 270 | 12 IP and 5 OP | £10,077 | |

IP, inpatient; OP, outpatient.

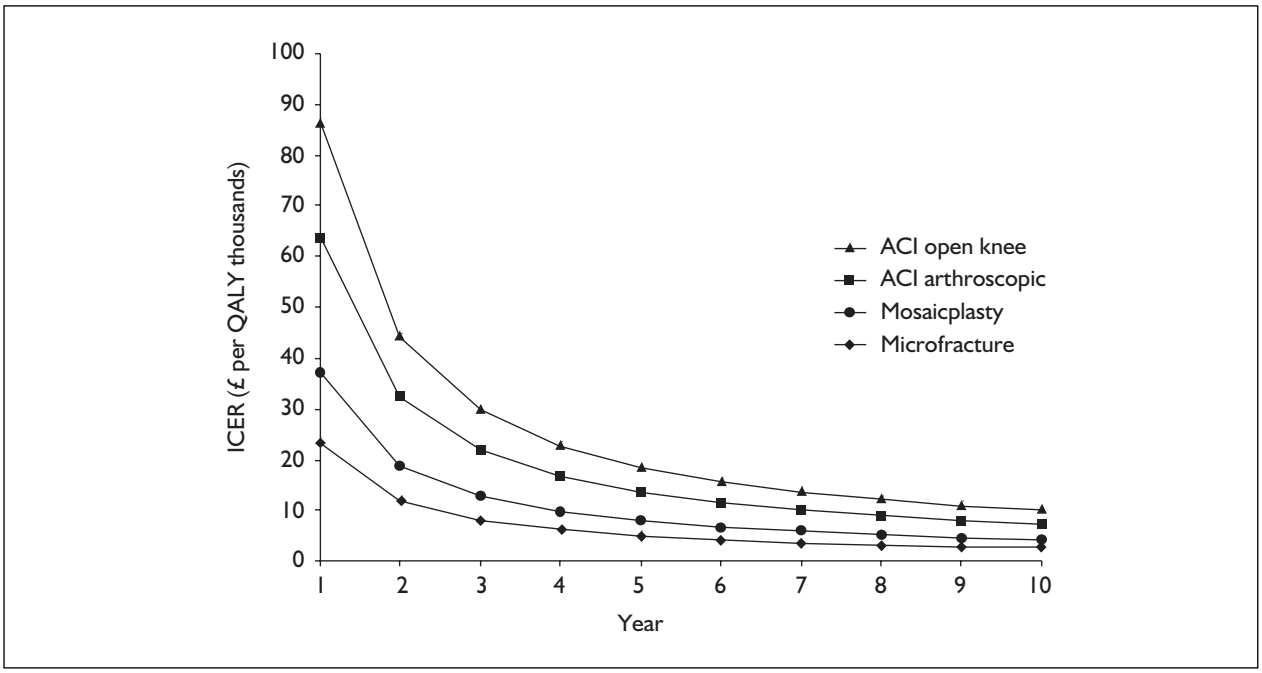


***FIGURE 2*** *ICERs: common annual quality of life increment of 0.1*

*[Confidential material removed]*

Consequently, the expert opinion of a quality of life gain of around 0.10 from the HTA monograph[2] is taken as the base case. This is similar to the value found by Minas from SF-36 data,[77] although his method of converting from SF-36 data to utility scores is not stated. Sensitivities of double (0.20) and half (0.05) this are applied in the analyses below.

The base case takes the quality of life improvement from successful treatment to be 0.1. As would be expected, given the common quality of life increment the exercise is one of cost minimisation and with microfracture being the least costly treatment it dominates the others.

*Figure 2* is mainly of interest as an illustration of how short a period is required for the maintenance of the quality of life gain for all the treatments to provide acceptable cost-effectiveness values, even with the conservative assumption of an improvement in quality of life of 0.1 over the period (discounting the health improvements at the Treasury-advised annual rate of 3.5%). This is a not unusual finding in surgical interventions because the interventions, and hence the cost, are often one-off events with lasting benefits.

A 0.1 improvement in the quality of life from successful treatment may be too conservative. If a greater improvement is applicable to ACI, it appears that it should also be applied to microfracture, as Knutsen's RCT results show that

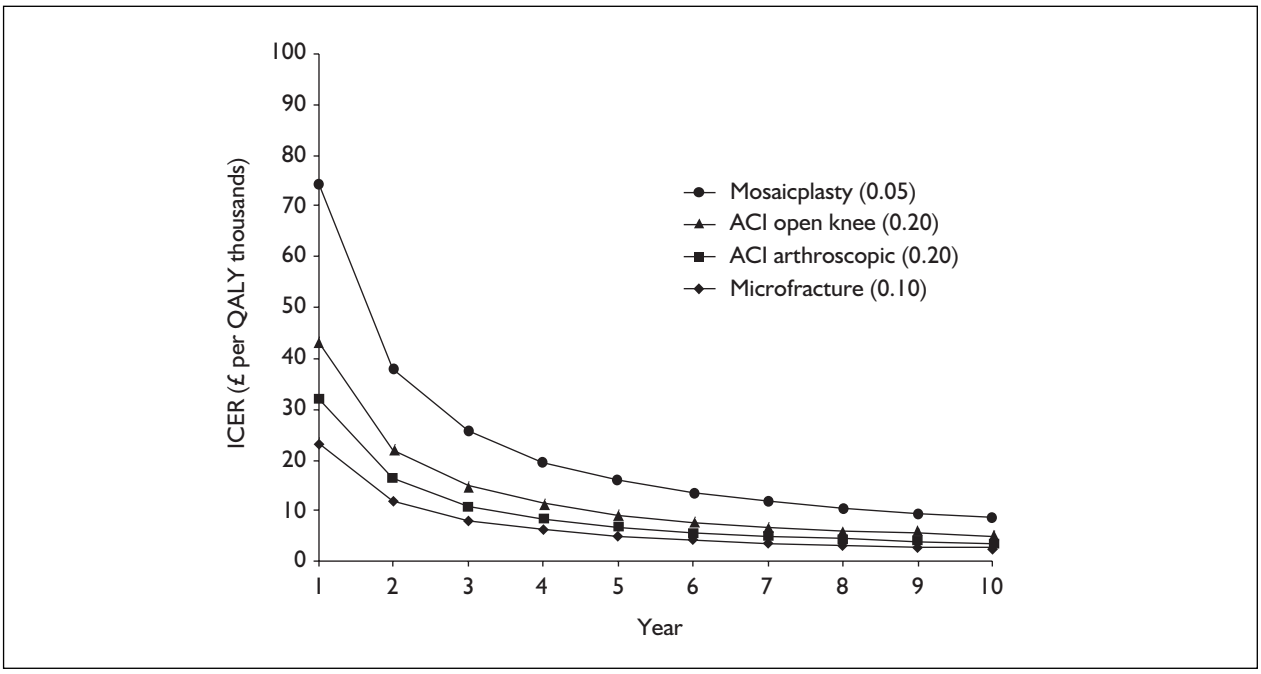


***FIGURE 3*** *ICERs: different quality of life increments*

***TABLE 4*** *Effects of different assumptions on QALY gain over time*

| | | QALY gain over lavage and débridement at year | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Intervention** | **Cost** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** |
| ACI open knee (0.20) | £8646 | 0.20 | 0.39 | 0.58 | 0.76 | 0.93 | 1.10 | 1.27 | 1.42 | 1.57 | 1.72 |
| ACI arthroscopic (0.20) | £6384 | 0.20 | 0.39 | 0.58 | 0.76 | 0.93 | 1.10 | 1.27 | 1.42 | 1.57 | 1.72 |
| Microfracture (0.10) | £2348 | 0.10 | 0.20 | 0.29 | 0.38 | 0.47 | 0.55 | 0.63 | 0.71 | 0.79 | 0.86 |
| Mosaicplasty (0.05) | £3710 | 0.05 | 0.10 | 0.14 | 0.19 | 0.23 | 0.28 | 0.32 | 0.36 | 0.39 | 0.43 |

what significant difference there is between microfracture and ACI would tend to favour microfracture.[63] Microfracture would still dominate ACI with these assumptions.

For illustrative purposes only, the 0.1 quality of life increment can be maintained for microfracture, with the values of 0.2 and 0.05 being applied to ACI and mosaicplasty, respectively (*Figure 3*, *Table 4*). Under these assumptions, microfracture naturally fares much worse, while the cost-effectiveness of ACI viewed in isolation rapidly approaches that of microfracture.

Given the assumptions, mosaicplasty is dominated, being both more expensive and less effective than microfracture. Similarly, given the assumption of equal effectiveness of open-knee and arthroscopic ACI, open-knee ACI is dominated as it is more expensive. The main consideration becomes between microfracture and arthroscopic ACI.

By assumption, the quality of life improvement from ACI in the above is double that of microfracture. As the cost of arthroscopic ACI is 170% greater than microfracture, when viewed in isolation it appears less cost-effective than microfracture. But if there was an additional quality of life gain of 0.1 of moving from microfracture to ACI, then that could justify an additional £4036 treatment cost, depending on for how long the additional quality of life gain was maintained.

The first two rows of *Table 5* present the cost-effectiveness ratios of moving from microfracture to ACI with an assumption of 0.1 and 0.2 quality of life increments for microfracture and ACI, respectively. The last two rows present the quality of life increment that would be need to be gained from arthroscopic ACI for a move from microfracture to arthroscopic ACI to be cost-effective.

***TABLE 5*** *ICERs and switching values for different assumptions*

| Microfracture vs ACI different QoL increment | Year 1 | Year 2 | Year 5 | Year 10 |
|---|---|---|---|---|
| Microfracture to ACI open knee | £62,980 | £32,032 | £13,477 | £7,317 |
| Microfracture to ACI arthroscopic | £40,360 | £20,527 | £8,637 | £4,689 |
| Switching value ACI arthroscopic QoL £30,000 per QALY | 0.22 | 0.17 | 0.12 | 0.11 |
| Switching value ACI arthroscopic QoL £20,000 per QALY | 0.29 | 0.20 | 0.13 | 0.12 |

***TABLE 6*** *Medium-term modelling – effects of assumptions on QALY gain over time*

| | | QALY gain over lavage and débridement at year | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Intervention | Cost | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| Mosaicplasty (0.05) | £3710 | 0.04 | 0.09 | 0.13 | 0.17 | 0.21 | 0.24 | 0.28 | 0.31 | 0.35 | 0.38 |
| ACI open knee (0.20) | £8646 | 0.17 | 0.33 | 0.49 | 0.64 | 0.79 | 0.93 | 1.06 | 1.20 | 1.32 | 1.45 |
| ACI arthroscopic (0.20) | £6384 | 0.17 | 0.33 | 0.49 | 0.64 | 0.79 | 0.93 | 1.06 | 1.20 | 1.32 | 1.45 |
| Microfracture (0.10) | £2348 | 0.08 | 0.16 | 0.23 | 0.30 | 0.37 | 0.44 | 0.51 | 0.57 | 0.63 | 0.69 |

For instance, in the above, if the quality of life gains are maintained for 2 years and if arthroscopic ACI gives a quality of life gain over microfracture of 0.10, the annual quality of life gain from arthroscopic ACI would have to be above 0.17 for it to be cost-effective at a threshold of £30,000 per QALY. At a more restrictive threshold of £20,000 per QALY, the quality of life gain would need to be above 0.20 for arthroscopic ACI to be cost-effective. The evidence does not suggest gains of that magnitude. However, if the quality of life gains persist into the medium term, the quality of life gain from arthroscopic ACI need be only slightly greater than that from microfracture to justify the relatively modest additional £4036 cost.

## Medium-term modelling

This seeks to extend the quality of life gains from ACI and its comparator treatments using the medium-term success rates reported in the case series from Peterson,[68–70] Steadman[72] and Hangody,[73] although it should be noted that Hangody's results for mosaicplasty are at only 4-year follow-up. One problem is that the progression of patients towards the reported success rates at around 10 years is unknown. For simplicity, the success rates of 85%, 80% and 88% for ACI, microfracture and mosaicplasty are applied to patients over a 10-year period, only those judged to be successes receiving the quality of life gains. This modelling does not impose any decay function on the data. In reality, there could be different times to best result (with ACI taking longer to mature than the others) and earlier declines (if there are declines) with some treatments than others.

As in the short-term modelling, if a common quality of life increment results from all treatments the slightly higher success rate with ACI over microfracture is not sufficient to justify the additional cost within a 10-year time horizon. The relatively high effectiveness with mosaicplasty owing to its 88% success rate does render it more cost-effective than microfracture for a threshold of £30,000 per QALY if this applies over 6 years, and for a threshold of £20,000 per QALY if this applies over 10 years. However, it should be borne in mind that Hangody's follow-up was at 4 years, that no decay function has been drawn from or imposed on the data, and an equal quality of life increment is required across successes from both treatments. Under these assumptions, mosaicplasty dominates ACI.

As in the short-term modelling, quality of life values of 0.20 and 0.05 can be applied for mosaicplasty and ACI, while retaining a value of 0.1 for microfracture (*Table 6*). Mosaicplasty again becomes dominated, and the choice lies between microfracture and ACI. The switching value is the quality of life gain required to justify a switch from microfracture to ACI (*Table 7*).

As costs have not changed, the absolute fall in the quality of life increase from applying an 85% success rate to ACI outweighs its relative improvement over the 80% success rate of microfracture. As a consequence, the quality of life

***TABLE 7*** *Medium-term modelling – ICERs and switching values for different assumptions*

| Microfracture vs ACI different QoL increment | Year 1 | Year 2 | Year 5 | Year 10 |
|---|---|---|---|---|
| Microfracture to ACI open knee | £71,568 | £36,400 | £15,315 | £8,314 |
| Microfracture to ACI arthroscopic | £45,864 | £23,326 | £9,814 | £5,328 |
| Switching value ACI arthroscopic QoL £30,000 per QALY | 0.26 | 0.18 | 0.13 | 0.11 |
| Switching value ACI arthroscopic QoL £20,000 per QALY | 0.33 | 0.22 | 0.15 | 0.12 |

increase necessary among ACI successes for moving from microfracture to ACI to be cost-effective is greater than if the 10-year success rates are not applied.

Given this, there is little point imposing a decay function. Unless this could be differentiated between treatments it would result in values somewhere between those in *Table 7* and that in the short-term modelling section.

Within both the short-term and the medium-term modelling, it should be borne in mind that in the only RCT of ACI against microfracture the only significant difference at 2 years was in the SF-36 physical functioning score, this tending to favour microfracture. (Knutsen and colleagues[63] were collecting further SF-36 scores within this RCT at 5-year follow-up in 2004.) The retrospective cohort study from Keele University found no significant difference in post-operative utility scores calculated from EQ-5D data between the ACI group and the mosaicplasty group, although the comparability of these groups and their pre-operative utilities are unknown. No generic measures of quality of life beyond 2 years' follow-up were uncovered by the literature search. Given the simple short- and medium-term modelling structure adopted, similar effectiveness data lead to microfracture dominating in cost-effectiveness terms as it is less expensive. Only a slightly greater quality of life gain would be necessary over a 10-year period for ACI to justify its greater treatment cost, but evidence for that is currently lacking.

## Long-term modelling

Long term modelling is hampered by a lack of long-term data as regards:

- the balance between quality of life successes and failures of the treatments under consideration, and whether these data refer to first or second line treatment
- the histology among treatment successes, as there is evidence that this changes over time. For example, it is known that after ACI, maturation of hyaline cartilage continues until 2 years: does it continue after that?
- the longevity of the benefits of treatment among the successes, and the incidences and the timings of osteoarthritis differentiated by patient histology: how much longer does hyaline last, and how long does mixed hyaline and fibrocartilage last, compared with predominantly hyaline and predominantly fibrocartilage?
- the timings and acceptance rates of TKR
- comparable quality of life measures between patient groups within treatments, not only between ACI, its comparator treatments and natural history, but also between the first/second line treatments under consideration and the quality of life before and after TKR.

Given that two of the long-term effects of successful treatment will be to improve quality of life and to avoid TKR, this last point has major implications for the assessment of the QALYs that will be gained or lost from the adoption of any one treatment regimen.

Because of the lack of data around key variables, a deterministic modelling structure was adopted, as outlined in *Figure 4*. Key structural assumptions are as follows.

- Only treatment in one knee needs to be modelled in the assessment of cost-effectiveness.
- Those classed as successes from first line treatment in terms of symptoms and quality of life can be divided into those with mainly hyaline cartilage (assumed to be durable) and those with non-hyaline cartilage (i.e. there are those with fibrocartilage giving short- and medium-term success, but not as durable, and leading to osteoarthritis in the longer term).
- Those classed as failures from first line treatment in terms of quality of life may be offered second line treatment in the light of an arthroscopic investigation.
- The effectiveness of second line treatments among failures is that same as that in first line treatments.

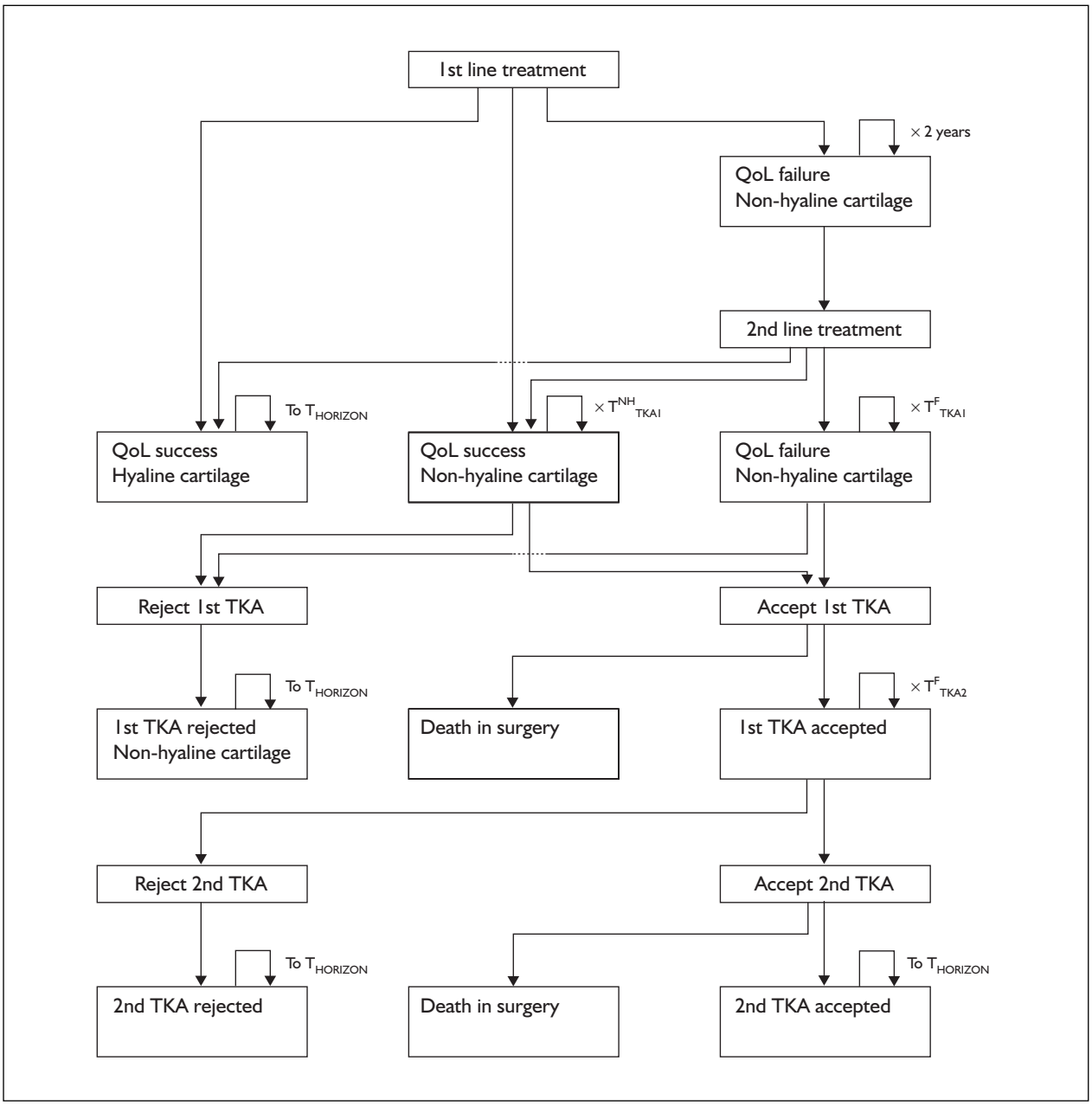


***FIGURE 4*** *ACI long-term model structure*

- A second line mosaicplasty cannot follow a first line mosaicplasty, nor can a second line microfracture follow a first line microfracture.
- Complete or near-complete hyaline cartilage prevents the onset of osteoarthritis.
- Non-hyaline cartilage breaks down over a specified period, resulting in osteoarthritis and patients being offered a first TKR.
- A proportion of patients may reject a first TKR.
- TKRs are of a specified longevity, after which patients are offered a second TKR, which again may be rejected.
- Other than the risk of death in TKR surgery, general population mortality risks apply.
- A 50-year time horizon is sufficient to capture all significant effects.

The model structure implies that the cost-effectiveness of treatments as a second line can be assessed in isolation. This could then be incorporated into the modelling of first line treatment in a recursive manner, provided that the combination of first and second line treatments is clinically permissible.

Given the assumption of equal treatment effectiveness (of permissible treatments) at first and second line, the simplest means of assessing treatments is to assess the cost-effectiveness of treatments in isolation; that is, as though there were no option of second line treatment. If a treatment proves to be the most cost-effective as the first line treatment, given equal treatment effectiveness it will also be the most cost-effective as the second line treatment, provided that this combination of treatments is permitted. If the combination is not permitted, the next most cost-effective treatment that is permitted will be the most cost-effective second line treatment. (The situation could occur that when assessed in isolation, moving from treatment A to treatment B might be cost-effective. But if treatment B cannot be followed by treatment A or by treatment B, treatment A followed by treatment B might be the most cost-effective feasible combination. Although possible, given the current circumstances this is of limited interest.)

Examining treatments as stand-alone first line treatments highlights their impact, without the complication of interpreting the balance between the impact of the first line treatment and the impact of second line treatment on the overall combined treatment cost-effectiveness. These are combined later to yield the absolute value of the combined treatments' cost-effectiveness.

Clinical effectiveness data are drawn from the clinical effectiveness section and are summarised in Appendix 4, while costs and quality of life relating to the treatments under consideration are as in the short-term modelling section, with the addition of the costs of TKR.

The model structure outlines how the main benefits of the treatments are the quality of life improvements as an immediate result of treatment, and longer term benefits in terms of avoiding osteoarthritis with its associated reduced quality of life and the requirement for TKR. To arrive at a figure for the total long-term QALY gain, the quality of life before and after TKR has to be related to the quality of life values already given for ACI and the other treatments.

Drewett and colleagues[85] used the Nottingham Health Profile and McGill Pain Questionnaire in 26 patients, transferring their results to the Rosser scale as in Gudex and Kind to calculate that quality of life rises from 0.910 before to 0.974 after TKR. However, their sample age range was from 49 to 84 years, with a mean age of 72.

James and colleagues[35] administered Rosser and EQ-5D among 30 TKR patients pre-operatively and post-operatively, but give few details as to the patient characteristics. They also asked the patients' consultants to complete the questionnaires to give the expert opinion values. Rosser resulted in an average gain of 0.044 among patients from an average pre-operative score of 0.868. The scores from consultants' Rosser scorings were 0.069 and 0.905, respectively. Patients' EQ-5D utility scores averaged 0.359 pre-operatively, with an average gain of 0.201, while those of consultants were 0.336 and 0.400 respectively. James notes that the Rosser scores showed slightly greater internal and between-groups consistency than the EQ-5D.

Lavernia and colleagues[86] report results from using the quality of well-being index among 116 TKRs, reporting an average improvement at 1 year of 0.072 and at 4 years of 0.055.

These quality of life results for TKR are difficult to align. In addition, the patient groups were generally of an older age group than would be the case in the patient group under consideration for ACI. The pre-operative Rosser values seem implausibly high, while those of EQ-5D may be rather low. The gains from EQ-5D may also be too high, particularly those of the consultants, which implies that patients would be willing to sacrifice more than half their remaining life expectancy in order to undergo TKR.

The initial assumption for modelling purposes takes a rough average of the above values, with TKR resulting in a quality of life gain of 0.1. It seems implausible that the quality of life after TKR is greater than that after successful ACI, microfracture or mosaicplasty, since knee replacement does not restore full function. In all likelihood it is less, but there is no information as to how much less. A plausible assumption is that TKR results in a quality of life similar to that among the initial patient group before ACI, microfracture or mosaicplasty (both groups being short of full function), with those that reject TKR lying somewhere in the middle (because the rejection is assumed to mean that their symptoms are not as bad as in those who accept). These assumptions are not intended as accurate estimates, but as a means of populating the model to show where the main uncertainties lie and which variables have the greatest effect on the cost-effectiveness of the treatments under consideration (*Table 8*).

The acceptance rates for TKR are speculative. As TKR is cost-effective both in the literature and

***TABLE 8*** *Long-term modelling: base-case assumptions*[a]

| **Quality of life**[b] | **QoL** | **QoL increment** | **QoL** |
|---|---|---|---|
| Pre-operative, post-débridement | 0.80 | | |
| Among successes | | 0.10 | 0.90 |
| Among failures | | 0.00 | 0.80 |
| Before TKR among those accepting TKR | | | 0.70 |
| After TKR among those accepting TKR | | 0.10 | 0.80 |
| Among those offered but rejecting TKR | | | 0.75 |
| **Treatment effectiveness** | **ACI** | **Microfracture** | **Mosaicplasty** |
| Successes with hyaline cartilage | 50% | 20% | 0% |
| Successes with mixed cartilage or fibrocartilage | 40% | 60% | 90% |
| Failures with mixed/fibrocartilage | 10% | 20% | 10% |
| **Total knee replacement** | | | |
| QoL deterioration period before TKR | 3 years | | |
| Time to first TKR among successes with hyaline cartilage | Never | | |
| Time to first TKR among successes with mixed/fibrocartilage | 15 years | | |
| Time to first TKR among failures with mixed/fibrocartilage | 15 years | | |
| Time to second TKR from first TKR | 15 years | | |
| TKR death rate | 1% | | |
| TKR acceptance rate | 50% and 100% | | |
| **Costs** | | | |
| ACI | £6,384 | Arthroscopic assumed | |
| Microfracture | £2,348 | | |
| Mosaicplasty | £3,710 | | |
| Arthroscopic investigation | £552 | | |
| First TKR | £5,417 | | |
| Second TKR | £10,077 | | |

[a] See Appendix 4 for details.

[b] Note that the absolute values for QoL are relatively unimportant. Rather it is their position relative to one another that affects results, i.e. the increments. Raising or lowering all QoL values but maintaining the absolute differences between them has little effect on modelling results. The minor effects that do arise are due to marginal differences in the numbers dying within TKR surgery between the different treatment strategies.

under the above assumptions, a lower acceptance rate will tend to worsen the cost-effectiveness of the first line treatments.

Modelling results are summarised in full in Appendix 5.

### *Base-case results for first line treatment*

With all those offered accepting TKRs, under the base-case assumption that only hyaline cartilage prevents osteoarthritis, the comparator of no further treatment after lavage and débridement results in all surviving patients receiving first and second line knee replacements. This also applies among those receiving mosaicplasty, although the quality of life under mosaicplasty is considerably higher than for débridement owing to its 90% success rate in creating a mixed or fibrocartilage repair.

A move from mosaicplasty to microfracture under the base-case assumptions results in around 20% of patients avoiding the need for TKR. There is both a quality of life gain from this and a gain in terms of the reduced costs of TKR. A move from microfracture to ACI involves another reduction in the number of patients requiring TKR, which is again associated with a quality of life gain and a reduction in the costs arising from TKR. However, the reduction in the cost of TKRs is not sufficient to outweigh the higher first line treatment costs of ACI, and taken together with the costs of TKRs it remains roughly as costly as mosaicplasty and somewhat more expensive than microfracture.

*Table 9* gives the cost-effectiveness of moving between treatments, and it is immediately obvious that since mosaicplasty does not produce any

***TABLE 9*** *Modelling results: base case*

| **Among 100 cohort** | **Débridement** | **ACI** | **Microfracture** | **Mosaicplasty** |
|---|---|---|---|---|
| QALYs (non-discounted) | 3465.8 | 3775.4 | 3646.5 | 3582.1 |
| **QALYs (discounted)** | **1785.9** | **1957.6** | **1901.2** | **1881.3** |
| First line cost | £0 | £638,400 | £234,800 | £371,000 |
| TKA costs (discounted) | £666,025 | £333,013 | £532,820 | £666,025 |
| **Total costs (discounted)** | **£666,025** | **£971,413** | **£767,620** | **£1,037,025** |
| First TKRs (non-discounted)[a] | 98.3 | 49.1 | 78.6 | 98.3 |
| Second TKRs (non-discounted)[b] | 90.7 | 45.4 | 72.6 | 90.7 |
| | 100% | of those offered accepting TKR | | |
| **Cost-effectiveness** | **Cost** | **QALYs** | **ICER** | |
| Débridement | £666,025 | 1785.9 | – | |
| Microfracture | £767,620 | 1901.2 | **£881** | |
| ACI | £971,413 | 1957.6 | **£3,617** | |
| Mosaicplasty | £1,037,025 | 1881.3 | **Dominated** | |
| **Among 100 cohort** | **Débridement** | **ACI** | **Microfracture** | **Mosaicplasty** |
| QALYs (non-discounted) | 3416.0 | 3750.5 | 3606.7 | 3532.4 |
| **QALYs (discounted)** | **1769.6** | **1949.4** | **1888.1** | **1865.0** |
| First line cost | £0 | £638,400 | £234,800 | £371,000 |
| TKA costs (discounted) | £248,731 | £124,365 | £198,985 | £248,731 |
| **Total costs (discounted)** | **£248,731** | **£762,765** | **£433,785** | **£619,731** |
| First TKRs (non-discounted) | 49.1 | 24.6 | 39.3 | 49.1 |
| Second TKRs (non-discounted) | 22.7 | 11.3 | 18.1 | 22.7 |
| | 50% | of those offered accepting TKR | | |
| **Cost-effectiveness** | **Cost** | **QALYs** | **ICER** | |
| Débridement | £248,731 | 1769.6 | – | |
| Microfracture | £433,785 | 1888.1 | **£1,561** | |
| Mosaicplasty | £619,731 | 1865.0 | **Dominated** | |
| ACI | £762,765 | 1949.4 | **£5,372** | |

[a] The number of patients within the cohort who undergo a first TKR. This has not been discounted. As the cohort is 100, these can also be seen as the percentage of patients who will be offered and accept a first TKR.
[b] As in the above, only the undiscounted number of patients who are offered and accept a second, replacement TKR, i.e. a replacement in the same leg.

reduction in the need for TKR, it is dominated by the less costly option of microfracture.

Microfracture compared with débridement alone appears extremely cost-effective, mainly because of the ineffectiveness of débridement. However, given the high cost of TKRs and their associated quality of life, coupled with the assumption that only hyaline cartilage prevents osteoarthritis and the need for TKRs, ACI also appears highly cost-effective.

Among a cohort of 100, if all offered TKR accept it the discounted quality of life gain relative to microfracture is around 56 QALYs for an additional cost of around £204,000: an ICER of £3617 per QALY. If only around half of those offered TKR accept it, the other half not being as affected, the discounted quality of life gain from ACI relative to microfracture is around 61 QALYs for an additional cost of around £330,000: an ICER of £5372 per QALY.

The effect of only 50% accepting TKRs, owing to the quality of life of those rejecting not being as detrimentally affected as those accepting, is to halve the number of first TKRs and quarter the number of second TKRs for each treatment strategy. TKR costs and total QALYs fall accordingly.

In quality of life terms, this tends to favour slightly treatments that require fewer TKRs. The quality of life increment of moving from microfracture to ACI increases to around 61 QALYs. In cost terms, the differences in the first line treatment costs become more significant.

As a consequence, the cost-effectiveness of moving from microfracture to ACI worsens slightly to £5372 per QALY. The quality of life argument, coupled with the greater importance of any differences in first line treatment costs, implies that mosaicplasty remains dominated by microfracture.

## Sensitivity analyses

Because of the uncertainty around many of the parameters of the modelling, a number of sensitivity analyses can be undertaken:

- the cost of ACI
- average time to TKRs
- quality of life gains from TKRs
- the success and biopsy data applied to first line treatments, coupled with changes to the assumptions as to what forms of cartilage prevent TKR.

In addition, when the TAR was commissioned the discount rates that were advised were 1.5% for health effects and 6.0% for financial effects. This advice has been amended to unify both rates at 3.5%, as in the Green Book from the Treasury. For completeness, the effects of applying the old discount rates have been presented. The full results of these are presented in Appendix 5 and the main points are summarised below.

### The costs of ACI and microfracture

Changes to the cost of ACI while retaining all other assumptions are best explored through the switching value. This is the cost to which the first line treatment for ACI would have to rise to make it too costly to be cost-effective. This in turn rests on the cost-effectiveness threshold that society is willing to pay. The results for two thresholds are presented in *Table 10*: £30,000 and £20,000 per QALY.

The base-case assumptions show a move from microfracture to ACI to be highly cost-effective. Given that the base-case assumptions give a cost for ACI arthroscopic surgery, cell culture and rehabilitation of £6384, the data in *Table 10* underline how high the cost of ACI would have to rise for it to cease to be cost-effective for the thresholds given.

For the switching values above, if the cost of ACI rises above these values, it ceases to be the most effective treatment, and microfracture becomes more cost-effective for the cost-effectiveness thresholds given.

Similarly, if the cost of microfracture falls, its relative cost-effectiveness improves. The cost estimate used was based on an assumption that microfracture involves an inpatient stay of 2 days, but in some places it may be done on an outpatient basis. If the cost of microfracture is half that stated in the base-case assumptions, the ICER for moving from microfracture to ACI rises from £3617 to £5701 per QALY if all those offered TKR accept. If only half accept, the ICER for moving from microfracture to ACI rises from £5372 per QALY in the base case to £7289 per QALY. The benefits from avoiding the need for TKRs, in terms of both cost and quality of life, are such that even if microfracture were costless, the ICER for moving from microfracture to ACI would still appear attractive: £7785 per QALY if all offered TKR accept, £9205 if only half accept.

### Time to total knee replacement

The time to onset of osteoarthritis and to TKR may differ from the base-case assumptions and may be rather longer than assumed. Lengthening this period to 20 years lengthens the period of quality of life improvement among non-hyaline successes. It also postpones the quality of life detriments associated with the period before TKR, and postpones the timing of any deaths in surgery. The costs of TKR are similarly postponed.

***TABLE 10*** *Switching values for cost-effectiveness thresholds*

| | £30,000 per QALY | £20,000 per QALY |
|---|---|---|
| All accept TKR | £21,200 | £15,600 |
| Half accept TKR | £20,900 | £15,340 |

Under the assumption that all those offered TKR accept it, the ICER for microfracture versus débridement rises from £881 to £1061 per QALY. The ICER of moving from microfracture to ACI rises from £3617 to £5443 per QALY. Mosaicplasty remains dominated.

If only half accept TKR, the figures for the ICER of moving from débridement to microfracture improve slightly: going from £1561 to £1480 per QALY. The ICER of moving from microfracture to ACI rises from £5372 to £6799 per QALY. Mosaicplasty remains dominated.

## Differing quality of life gains

There are no data on the quality of life among those receiving TKRs relative to those receiving first line treatment for chondral lesions. The base case is that those undergoing first line treatments have an initial quality of life of 0.8, which if surgery is a success rises by 0.1 to 0.9. If the first line treatment is a failure their quality of life remains at 0.8. The assumption among those being offered and accepting TKRs is that their quality of life decays to 0.7 over a 3-year period which, provided they survive TKR surgery, rises by 0.1 to 0.8. (Owing to data deficiencies the period of 3 years is entirely arbitrary. Lengthening the period of decline would slightly increase the differences in the aggregate QALY values.)

Introspection suggests that the quality of life gains from TKR may be greater than that from the first line treatments for chondral lesions, because TKR is carried out for advanced osteoarthritis. The initial quality of life among TKR patients could be reduced to 0.6, and an increase in gain to 0.2 allowed. The effect of this would be to reduce the aggregate quality of life among the various treatment options. The effect on cost-effectiveness is muted. Under the assumption that all those offered TKR accept it, the ICER for microfracture falls marginally from £881 to £853 per QALY. The ICER of moving from microfracture to ACI falls from £3617 to £3280 per QALY. Mosaicplasty remains dominated.

Allowing for the possibility of less severe osteoarthritis and only half accepting TKRs, the base case assumed a quality of life among these of halfway between the pre-operative and post-operative quality of life among TKR accepters: 0.75. Adopting a similar approach implies a quality of life among TKR rejecters of 0.70. Again, the effects are relatively muted. For microfracture the ICER falls from £1561 to £1453 per QALY. The ICER of moving from microfracture to ACI falls from £5372 to £4415 per QALY. Mosaicplasty remains dominated.

## Previous discount rates

Applying the old discount rates of 1.5% for health effects and 6.0% for financial has two effects:

- A higher success rate implies greater aggregate quality of life to the time of first knee replacements. To the extent that a higher success rate is due to a greater proportion of hyaline repairs, it also implies fewer TKRs. As a result, the long-term quality of life gains from this become more significant when discounting health effects at only 1.5% instead of 3.5%.
- There is also a financial effect related to the number of hyaline repairs, in that a lower number of TKRs implies a lower long-term cost. Discounting financial effects at 6.0% instead of 3.5% makes these financial savings from hyaline repairs less important.

Under the assumption that all those offered TKR accept it, for microfracture, given its low rate of hyaline successes, the ICER of moving to it from débridement rises from £881 to £1057 per QALY. Partly as a result of the more poorly performing microfracture, but also owing to its higher hyaline success rate, the ICER of moving from microfracture to ACI falls slightly from £3617 to £3200 per QALY. Mosaicplasty remains dominated.

If only half of those offered TKR accept it, the detrimental effects of non-hyaline repairs are lessened, as those rejecting TKR presumably do so on grounds of acceptable quality of life. The ICER for microfracture falls from £1561 to £1337 per QALY. The ICER of moving from microfracture to ACI falls from £5372 to £3654 per QALY, but remains above the value were all to accept TKR. Mosaicplasty remains dominated.

## Different success rates and biopsy data: Knutsen data

The sensitivity analyses outlined above show the effects of altering what could be labelled as interim parameters within the model. Parameters of first order importance are the success rates of the different treatments, coupled with what the biopsy data imply for the requirement for TKRs. An alternative RCT source of success rates and biopsy data for microfracture and ACI is the paper by Knutsen and colleagues[63] (*Table 11*).

Grouping biopsies where the biopsy either was insufficient to make a judgement or showed no

***TABLE 11*** *Clinical outcomes from Knutsen trial*[63]

| | | | Biopsy data | | | |
|---|---|---|---|---|---|---|
| | **Success** | **Failure** | **Hyaline** | **Mixed** | **Fibrocartilage** | **Unknown/nil** |
| ACI | 95.0% | 5.0% | 6/32 | 10/32 | 11/32 | 5/32 |
| Microfracture | 97.5% | 2.5% | 4/35 | 6/35 | 18/35 | 7/35 |

***TABLE 12*** *Switching values for different assumptions about need for TKR with fibrocartilage*

| **All accept TKR** | **£30,000 per QALY** | **£20,000 per QALY** |
|---|---|---|
| Mixed repair avoids TKR | £12,800 | £9,800 |
| Mixed repair requires TKR | £5,310 | £4,480 |

repair is unhelpful. However, given the relative success rates of ACI and microfracture, there is no reason to believe that this group would tend to favour one treatment if it was disaggregated into those showing no repair and those with an insufficient biopsy. Consequently, this group has been ignored in the following.

Retaining the assumption of hyaline cartilage preventing the onset of osteoarthritis and the need for TKRs, two sensitivity analyses can be performed applying the above biopsy data to the treatment success rates:

- A repair of a mixture of hyaline and fibrocartilage proceeds to osteoarthritis and TKR, as does a repair of fibrocartilage.
- A repair of a mixture of hyaline and fibrocartilage prevents osteoarthritis and TKR, while a repair of fibrocartilage proceeds to osteoarthritis and TKR.

The truth may be somewhere between these two analyses, depending on the balance between hyaline cartilage and fibrocartilage in the repairs of the mixed group.

Under the assumption that a mixed repair still results in osteoarthritis and TKR this slightly worsens the balance for microfracture relative to the base case. However, the main effect is on ACI as this hugely reduces the successes among whom osteoarthritis is prevented, from 50% in the base case to less than 20%.

As a consequence, under the assumption that all offered TKR accept it, the ICER for microfracture rises from £881 to £1140 per QALY, but the ICER of moving from microfracture to ACI rises from £3617 to £42,858 per QALY.

If only 50% accept TKR, for microfracture the ICER rises from £1561 to £1578 per QALY. The ICER of moving from microfracture to ACI rises from £5372 to £40,708 per QALY.

Changing to the assumption that a mixed repair is sufficient to prevent osteoarthritis, the Knutsen data become much closer in effect to the base-case values. In consequence, under the assumption that all those offered TKR accept it, the ICER for microfracture falls from £881 to £18 per QALY. The ICER of moving from microfracture to ACI rises from £3617 to £8659 per QALY.

If only 50% accept TKR, for microfracture the ICER falls from £1561 to £914 per QALY. The ICER of moving from microfracture to ACI rises from £5372 to £10,421 per QALY.

Switching values for the cost of ACI can again be computed as under the base case, only this time using Knutsen's biopsy data (*Table 12*). If a mixed repair avoids the need for TKR, while the Knutsen data are worse than the base case for ACI, the cost of ACI would still have to rise by 50–100% for it to cease to be cost-effective. However, if only a hyaline repair is sufficient to avoid TKR and Knutsen's biopsy data apply, microfracture is more cost-effective. The cost of ACI would have to fall somewhat for it to become cost-effective.

## First and second line treatments

As already noted, there is no information as to the relative effectiveness of treatments in first and second line use. The only feasible assumption for the base case is to assume them to be the same. Consequently, the most cost-effective treatment as a first line treatment will also be the most cost-effective as a second line treatment, provided that the combination of first and second line

treatments is permitted. Furthermore, on the assumption of a cost-effective first line treatment being available, applying this as a second line treatment with an assumption of equal effectiveness will necessarily improve cost-effectiveness ratios compared with the first line treatment in isolation. These are presented in Appendix 5, more for analytical completeness than as an accurate estimate of the use of treatments as a second line among treatment failures.

As ACI appears cost-effective as a first line treatment under the base-case assumptions, it will be cost-effective as a second line treatment to mosaicplasty, microfracture and ACI. Given that second rounds of mosaicplasty and microfracture may be undesirable or unfeasible, despite the uncertainty surrounding the cost-effectiveness estimates, the least uncertainty may be that surrounding the cost-effectiveness of ACI as a second line treatment.

## Conclusions from economic analysis

Within the literature, the assessment of quality of life gains from the treatments for chondral lesions under consideration is limited to around 2 years. Within SF-36 data, ameliorating the effects of these lesions appears to improve the physical, mental and social functioning scores. However, there are limited data distinguishing these scores between different treatments and what data there are do not show a convincing significant difference between the treatments under consideration in favour of ACI.

The data as presented within the literature do not permit QALYs to be calculated, and as a consequence the modelling of this section has had to fall back on the previous work of Jobanputra and colleagues[81] and assume a quality of life increment of 0.1 in the base case for all treatment successes. This ties in with the value stated by Minas[77] as having been calculated from SF-36 data for ACI, although there is no indication of how he arrives at this value.

Since open-knee ACI is more expensive than arthroscopic ACI, in the absence of any data suggesting it to be more cost-effective than arthroscopic ACI, open-knee ACI is dominated in terms of cost-effectiveness and has been largely disregarded in this section.

Simple short-term modelling shows that the quality of life gain from ACI relative to microfracture would have to be between 70 and 100% greater over 2 years for it to be more cost-effective within the £30,000 to £20,000 per QALY cost-effectiveness thresholds. However, if the quality of life gains are maintained for a decade, the quality of life increment from ACI relative to microfracture would only have to be 10–20% greater to justify its additional cost within the £30,000 to £20,000 per QALY cost-effectiveness band.

Long-term modelling of the cost-effectiveness of mosaicplasty, microfracture and ACI is hampered by a lack of long-term data. The principal long-term benefits can be characterised as the avoidance of osteoarthritis and TKR among those with a hyaline repair to their lesion. Mosaicplasty performs consistently poorly under this assumption, as all repairs will have fibrocartilage around the plugs and so lead to osteoarthritis.

Under the base-case assumptions as outlined in Appendix 5, ACI performs relatively well compared with microfracture. Under the base case, the cost-effectiveness of moving from microfracture to ACI is between £3500 and £5500 per QALY, which is well within cost-effectiveness thresholds. The cost of ACI would have to rise dramatically for this to cease to be the case.

Changing the time to TKR among failures and those with non-hyaline repairs has relatively little impact on the cost-effectiveness of ACI, as does the quality of life gain from TKR.

As would be expected, the quality of life gain among treatment successes has a major impact on the cost-effectiveness of ACI. Given its higher assumed success rate and higher assumed rate of hyaline successes, a higher quality of life among successes further improves the cost-effectiveness of ACI relative to microfracture.

However, the key data upon which the long-term model is constructed are subject to considerable uncertainty. The treatments' effectiveness data and biopsy data vary among studies, and it is unclear as to the need for and time to TKR among those with mixed cartilage repairs. Applying the biopsy data of Knutsen results in hugely different estimates of the cost-effectiveness of ACI. Knutsen's biopsy data see a far higher proportion of ACI patients having a mixed rather than a pure hyaline repair. If these mixed repairs later develop

osteoarthritis and the need for TKR, ACI does not appear to be cost-effective.

In short, there is great uncertainty as to:

- the medium- to long-term effectiveness of the three treatments under consideration
- the medium- to long-term prognosis for repairs of hyaline cartilage, mixed and fibrocartilage
- the quality of life among chondral treatment successes and failures
- the quality of life among those undergoing TKRs relative to those undergoing chondral treatment successes and failures.

The first three bullet points are of critical importance to any modelling, and the projections of this section can only be viewed as tentative.

ACI shows great promise as a treatment for chondral lesions, and the projection of this section suggests a potential for it to be highly cost-effective. At present, this has not been demonstrated. If the clinical effectiveness of ACI among failures from other treatments is similar to that as a first line treatment, there is less uncertainty around the cost-effectiveness of ACI as a second line treatment, given the limited combination of first and second line treatments that are permitted.

# Chapter 5

# Discussion, decision analysis and research needs

## Clinical effectiveness

Since the last appraisal by NICE, the evidence base has been improved by a number of RCTs. However, some problems remain. First, and inevitably, follow-up from these is as yet quite short-term. It appears that all interventions are mostly successful in the short-term. Second, results in the trials differ, with Knutsen and colleagues[63] finding fibrocartilage in biopsies after ACI, whereas Briggs and colleagues[66] found hyaline in about half. Third, the distinction between hyaline cartilage and fibrocartilage may be too crude; more sophisticated ways of assessing the quality of regenerating cartilage may provide better predictors of later success.

The crucial issue is the durability of the repair, and the extent to which a repair consisting of mostly hyaline will prevent later osteoarthritis and reduce the need for knee replacements, compared with those consisting mostly of fibrocartilage. We do not have the answer to this yet.

Another issue is whether a repair, even a perfect one, will prevent osteoarthritis in this group of patients. Will they return to full activity and then incur future injuries? The study by Messner and Meletius[17] is of interest here. They found signs of osteoarthritis in previously injured knees, but also, although to a lesser extent, in the patients' other knees. Is there a group of patients who are injury prone, or just engaged in levels of activity more than their knee joints can withstand?

## Cost-effectiveness

As emphasised in Chapter 4, it is not possible to produce a reliable cost per QALY, because the necessary data are not available. Ideally, the following are needed:

- data on the absolute benefits of ACI compared with the natural history of untreated lesions, as well as on the benefits relative to other forms of treatment such as microfracture
- long-term follow-up, sufficient to determine the frequency and timing of symptoms, and the need for and timing of knee replacement, after each treatment option.

All we can do is provide some speculative analysis based on a range of assumptions. It is up to the reader to decide how reasonable these assumptions are. However, many of the ICERs are quite low compared with those in other NICE appraisals, and even quite marked divergence from the assumptions used would leave the ICERs within the NICE range of acceptability.

One of the key issues is the cost of the cells. If they cost £300 rather than over £3000, there would be little argument. If ACI became a routinely available NHS intervention, could there be NHS facilities, similar to those at Oswestry? How much might the cost of cells fall? Different manufacturers quote different prices for cells; BBraun gave an average price of £4000, Verigen £3500 basic, but with discounts for volume.

## Decision options

A conservative, scientifically purist view would be that NICE should not approve ACI until better evidence from long-term follow-up is available. This evidence would be on long-term development of osteoarthritis and the rate of knee replacements. This should be available in about 20 years. In the meantime, taking this line and rejecting ACI would provide certainty that the NHS was not wasting funds on a procedure of unproven cost-effectiveness.

However, if ACI was then shown to be a good buy for the NHS, for 20 years patients would have been treated with less effective procedures, and many of these patients would have developed osteoarthritis. The liberal but leap-of-faith argument is therefore that we should give ACI the benefit of the doubt, bring it into routine use and expect to be reassured of the correctness of this decision by a lack of osteoarthritis in the cohort of treated people.

One approach used in Australia[87] has been the 'interim funding' system, used when the evidence on benefits and costs is borderline, but the technology looks potentially successful. Various restrictions are placed on the roll-out, such as limiting the number of sites at which the

technology is provided, having clear indications for treatment and requiring collection of a standard data set. Interim funding is for up to 3 years.

The situation with ACI has similarities with the assessment of new forms of joint prosthesis. If the advantage of a new prosthesis is greater longevity, it could require a 15-year-long RCT to show benefit. Two methods of obtaining quicker answers have been tried. The first is to look for ways of early detection of failure, for example by the use of radio-opaque markers adjacent to the prosthesis that can detect signs of movement, or by bone density measurement around the prosthesis, again to detect signs of loosening. The second is by modelling: to consider the extra cost of the new prosthesis, and to consider how much better it would have to be to justify that cost. If the extra benefit required was so great that it would be unlikely to be achieved, then the new prosthesis is not likely to be cost-effective (at that price). This has been done for hip replacements by Gillespie and colleagues.[88]

Are there ways in which a short-term study (perhaps 5 years or so) could predict the durability and longevity of cartilage repairs? The key comparison appears to be between microfracture and ACI, although a natural history arm would give data with which to assess absolute benefit. If microfracture is taken as current standard treatment, there is no RCT evidence to quantify its benefit over no surgical treatment, or over débridement alone.

If such methods exist, NICE could adopt a middle way, allowing ACI under controlled conditions with data collection, or as part of a longer RCT against microfracture, with a view to being able to produce a more informed appraisal in the medium term, rather than after 20 years.

Any such study would have to be designed to cope with evolving technologies. Recently, changes have been in the shift from open surgery to arthroscopic ACI, coupled with development of new membranes or caps.

### Implementation issues

One scheme already exists, provided by one of the manufacturers, whereby surgeons new to the procedure are trained.

## Recommendations for research

- As outlined above, there is a need for methods to predict long-term results at an earlier stage.
- Not all patients receiving ACI end up with all or mostly hyaline cartilage. How can results be improved? The main problems in tissue engineering approaches to cartilage have been summarised (Aspden R, Institute of Medical Sciences, University of Aberdeen, UK, August 2004; personal communication) as:
  - to produce hyaline cartilage rather than fibrocartilage
  - to reproduce the structural organisation within that cartilage
  - to encourage that tissue to have the right mechanical properties
  - to integrate the repair with surrounding tissue.

Further basic research is needed on the genes and molecules that influence stem cells to become chondrocytes, such as cartilage growth factors. There is also a need for research to develop methods that improve the integration of chondrocytes into cartilage.

- Conversely, after microfracture, a minority of patients receive a mostly hyaline repair. Are there ways, perhaps involving influencing stem cell development, whereby that proportion could be increased?
- What is the best method for classifying the cartilage in the repair? Can biopsy be avoided? There have been mixed results in reports of the use of MRI in cartilage lesions. Gelb and colleagues in 1996[89] concluded that MRI had low sensitivity for chondral lesions, whereas in 2003 Roberts and colleagues[90] found better results. (Roberts and colleagues also noted the quality of cartilage increasing over time.) Brown and colleagues found that sensitive MRI could show better results with ACI than with microfracture, although this was not from an RCT.[91] The different findings may reflect advancing MRI technology.
- There may be an issue about dedifferentiation of chondrocytes in culture. This was at one time raised as a possible cancer scare (for which there is no evidence), but the main question is whether dedifferentiated cells are capable of forming healthy cartilage, and whether different systems of culture might be more suited to minimising dedifferentiation.
- Other issues include the optimum number of cells to be implanted, and whether it is safe to freeze cells at first (diagnostic) arthroscopy, to avoid the need for an additional procedure to harvest the cells. Minas[92] reports freezing the sample for periods ranging from 6 weeks to 2 years. Using a lower number of cells may reduce cost, but might also give a poorer result.

- The distinction between hyaline cartilage and fibrocartilage is probably too crude, and more sophisticated ways of assessing the nature and quality of regenerating cartilage would be useful.
- The Chartered Society of Physiotherapy, in its submission to NICE, noted the range of rehabilitation regimens used, and in particular that the early weight-bearing in the trial by Bentley and colleagues contrasted with the much later (8–12 weeks) weight-bearing in the trials by Knutsen and colleagues[63] and Horas and colleagues.[65] Does this suggest that early weight-bearing may encourage the formation of hyaline cartilage? Trials of different rehabilitation systems are indicated.

## Conclusion

This report concludes with the words that NHS policy makers least want to hear, but that academics often resort to in situations of uncertainty, and which seem appropriate in this case: 'more research is necessary'.

# Acknowledgements

We thank the following for information or advice, but absolve them from any errors in this report, responsibility for which rests solely with the Aberdeen TAR team: Professor Richard Aspden (University of Aberdeen), Professor George Bentley, (Royal National Orthopaedic Hospital, Stanmore), Mr James Bidwell (Consultant Orthopaedic Surgeon, Aberdeen Royal Infirmary), Mr Tim Briggs (Royal National Orthopaedic Hospital, Stanmore), Miss Helen Campbell (Health Economics Research Group, Oxford), Mr Richard Harvey (Management Accountant, Southampton University Hospitals Trust), Professor David Rowley (University of Dundee), Francis Ruiz (NICE) and Mr Derek Walker (Management Accountant, Grampian University Hospitals). We thank Lynn Robertson for secretarial assistance and Zahra Bakhtiar for library assistance.

We acknowledge useful research suggestions made to NICE by the British Society for Rheumatology and the Chartered Society of Physiotherapy.

## Contribution of authors

Literature searches were done by Lynda Bain (Information Scientist). The review of clinical effectiveness was led by Christine Clar (Researcher in Systematic Reviews), assisted by Linda McIntyre (Systematic Reviewer), Sian Thomas (Systematic Reviewer) and Norman Waugh (Professor of Public Health). Exploratory modelling was done by Ewen Cummins (Health Economist) and John Lamb (Lecturer in Management Studies). Ewen Cummins wrote the economic chapters, assisted by Norman Waugh. The first chapter is an updated version of the chapter from the previous report by Paresh Jobanputra (Consultant Rheumatologist) and colleagues, revised by Norman Waugh assisted by Paresh Jobanputra. The discussion chapter was written by Norman Waugh. All authors commented on the draft. Norman Waugh is guarantor.

## About the Aberdeen HTA group

The Aberdeen Health Technology Assessment Group is part of the Institute of Applied Health Sciences (IAHS), which is part of the College of Medicine and Life Sciences of the University of Aberdeen. The HTA Group carries out independent health technology assessment reports (TARs) for the UK HTA Programme, which commissions TARs for the National Institute for Health and Clinical Excellence (NICE) and other bodies, such as the National Screening Committee. The group is multidisciplinary and draws on individuals' backgrounds in public health, health services research, information science and health economics, supplemented by clinical input as appropriate.

The Institute of Applied Health Sciences is made up of discrete but methodologically related research groups. The HTA Group is drawn mainly from the Health Services Research Unit, Public Health and the Health Economics Research Unit.

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# Appendix 1

## Commonly used clinimetric scoring systems for assessment of knee disorders

***TABLE 13*** *Scoring systems*

| Scale | Description |
|---|---|
| Lysolm Score[93] (100 = best, 0 = worst) | Scores completed with patient collaboration. Items include limp, requirement for a support (e.g. crutch), stair-climbing, squatting, walking, running and jumping, pain, swelling and thigh atrophy |
| Noyes (Cincinnati)[94] Symptom rating scale (10 = best, 0 = worst) | Six patient categories, e.g. normal knee, able to work and do sport with jumping, hard pivoting is graded 10 points, severe unrelieved symptoms with activities of daily living graded 0 points. A sports rating scale (100–0), functional scale assessing daily living activity (120–0), sporting activity (100–0) and aspects of clinical examination such as pivot shift test, degree of crepitus and range of motion may also be incorporated in a detailed scheme for final rating |
| Knee Society Scoring System[95] (200 = best, 0 = worst) | The goal of this scoring system is to evaluate the outcome of knee arthroplasty. Assesses pain, function, i.e. walking, stair-climbing, and clinical features such as range of motion, stability, alignment, flexion contracture and extension lag. The assessment consists of two components: a knee rating system which includes pain (50 points), stability (25) and range of motion (25), and a functional assessment which considers walking distance (50 points) and stair-climbing (50 points) with deductions for the use of walking aids |
| Hospital for Special Surgery[96] (100 = best, 0 = worst) | Scores determined from symptom severity and clinical examination. The following features are included: function including walking, transferring and climbing stairs (22 points), pain (30 points), range of motion (18 points), muscle strength (10 points), deformity (10 points) and instability (10 points) |
| International Knee Documentation Committee[97] (100 = best, 0 = worst) | The following items are rated (according to the scale: normal, nearly normal, abnormal and severely abnormal): patient assessment of function, symptoms, range of motion and ligament examination |

# Appendix 2

## Outerbridge classification system for cartilage defects

***TABLE 14*** *Outerbridge system*[50]

| Grade | Description |
|---|---|
| I | Softening or swelling of cartilage |
| II | Fragmentation or fissuring in an area 0.5 inches in diameter or less |
| III | Same as grade II but an area greater than 0.5 inches in diameter |
| IV | Erosion of cartilage down to bone |

0.5 inches = 12.7 mm.

# Appendix 3

## Search strategies

### MEDLINE

#### 2000 to 22 June 2004

1. exp CHONDROCYTES/tr [Transplantation]
2. exp TRANSPLANTATION, AUTOLOGOUS/
3. (chondrocyte$ and transplant$).mp.
4. (chondrocyte$ and implant$).mp.
5. chondrocyte transplantation.mp.
6. chondrocyte implantation.mp.
7. cartilage graft$.mp.
8. exp Cell Transplantation/
9. exp CARTILAGE, ARTICULAR/su, tr, in [Surgery, Transplantation, Injuries]
10. exp CARTILAGE/su, tr, in [Surgery, Transplantation, Injuries]
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. exp Knee Injuries/
13. exp Knee Joint/
14. exp Osteochondritis Dissecans/
15. exp PATELLA/
16. exp Cartilage Diseases/
17. cartilage defects.mp.
18. exp OSTEOARTHRITIS, KNEE/su, th [Surgery, Therapy]
19. exp ARTHROSCOPY/
20. exp Athletic Injuries/
21. (osteochondral fracture$ or chondral fracture$).mp.
22. exp KNEE/
23. knee$.mp.
24. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25. 11 and 24
26. limit 25 to yr=2000-2004
27. randomized controlled trial.pt.
28. controlled clinical trial.pt.
29. randomized controlled trials/
30. random allocation/
31. double-blind method/
32. single-blind method/
33. 27 or 28 or 29 or 30 or 31 or 32
34. limit 33 to animal
35. limit 33 to human
36. 34 and 35
37. 34 not 36
38. 33 not 37
39. clinical trial.pt.
40. exp clinical trials/
41. clin$ with trial$.tw.
42. placebos/
43. placebo$.tw.
44. random$.tw.
45. exp research design/
46. 39 or 40 or 41 or 42 or 43 or 44 or 45
47. limit 46 to animal
48. limit 46 to human
49. 47 and 48
50. 47 not 49
51. 46 not 50
52. comparative study/
53. exp evaluation studies/
54. follow-up studies/
55. prospective studies/
56. (control$ or prospectiv$ or volunteer$).tw.
57. 52 or 53 or 54 or 55 or 56
58. limit 57 to animal
59. limit 57 to human
60. 58 and 59
61. 58 not 60
62. 57 not 61
63. 38 or 51 or 62
64. 26 and 63

### MEDLINE

#### 1996–2004

1. mosaicplasty.mp.
2. autologous osteochondral transplantation.mp.
3. autologous osteochondral transplantation.tw.
4. (osteochondr$ and transplant$).mp.
5. autologous osteochondral implantation.mp.
6. autologous osteochondral implantation.tw.
7. 1 or 2 or 3 or 4
8. exp KNEE JOINT/ or exp KNEE/ or exp KNEE INJURIES/
9. exp PATELLA/
10. 8 or 9
11. 7 and 10
12. randomized controlled trial.pt.
13. controlled clinical trial.pt.
14. randomized controlled trials/
15. random allocation/
16. double-blind method/
17. single-blind method/
18. 12 or 13 or 14 or 15 or 16 or 17
19. limit 18 to animal
20. limit 18 to human

21. 19 and 20
22. 19 not 21
23. 18 not 22
24. clinical trial.pt.
25. exp clinical trials/
26. clin$ with trial$.tw.
27. placebos/
28. placebo$.tw.
29. random$.tw.
30. exp research design/
31. 24 or 25 or 26 or 27 or 28 or 29 or 30
32. limit 31 to animal
33. limit 31 to human
34. 32 and 33
35. 32 not 34
36. 31 not 35
37. comparative study/
38. exp evaluation studies/
39. follow-up studies/
40. prospective studies/
41. (control$ or prospectiv$ or volunteer$).tw.
42. 37 or 38 or 39 or 40 or 41
43. limit 42 to animal
44. limit 42 to human
45. 43 and 44
46. 43 not 45
47. 42 not 46
48. 23 or 36 or 47
49. 11 and 48

## MEDLINE

### 1996–2004

1. exp CHONDROCYTES/tr [Transplantation]
2. exp TRANSPLANTATION, AUTOLOGOUS/
3. (chondrocyte$ and transplant$).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
4. (chondrocyte$ and implant$).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
5. chondrocyte transplantation.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
6. chondrocyte implantation.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
7. cartilage graft$.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
8. exp Cell Transplantation/
9. exp CARTILAGE, ARTICULAR/su, tr, in [Surgery, Transplantation, Injuries]
10. exp CARTILAGE/su, tr, in [Surgery, Transplantation, Injuries]
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. exp Knee Injuries/
13. exp Knee Joint/
14. exp Osteochondritis Dissecans/
15. exp PATELLA/
16. exp Cartilage Diseases/
17. cartilage defects.mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
18. exp OSTEOARTHRITIS, KNEE/su, th [Surgery, Therapy]
19. exp ARTHROSCOPY/
20. exp Athletic Injuries/
21. (osteochondral fracture$ or chondral fracture$).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
22. exp KNEE/
23. knee$.mp.
24. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25. 11 and 24
26. ECONOMICS/
27. "Costs and Cost Analysis"/
28. Cost Allocation/
29. Cost-Benefit Analysis/
30. Cost Control/
31. Cost Savings/
32. Cost of Illness/
33. Cost Sharing/
34. "Deductibles and Coinsurance"/
35. Medical Savings Accounts/
36. Health Care Costs/
37. Direct Service Costs/
38. Drug Costs/
39. Employer Health Costs/
40. Hospital Costs/
41. Health Expenditures/
42. Capital Expenditures/
43. Value of Life/
44. exp Economics, Hospital/
45. exp Economics, Medical/
46. Economics, Nursing/
47. Economics, Pharmaceutical/
48. exp "Fees and Charges"/
49. exp BUDGETS/
50. (low adj cost).mp.
51. (high adj cost).mp.
52. (health?care adj cost$).mp.
53. (fiscal or funding or financial or finance).tw.
54. (cost adj estimate$).mp.
55. (cost adj variable).mp.
56. (unit adj cost$).mp.
57. (economic$ or pharmacoeconomic$ or price$ or pricing).tw.
58. or/26-57
59. 25 and 58

## MEDLINE

### 1966–2004

1. quality of life.mp. or exp "Quality of Life"/
2. quality adjusted life year.mp. or exp Quality-Adjusted Life Years/
3. Qaly.tw.
4. Health utility.tw.
5. EuroQol.tw.
6. SF-36.tw.
7. Rosser.tw.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. knee$.tw.
10. KNEE JOINT/ or KNEE/ or KNEE INJURIES/ or ARTHROPLASTY, REPLACEMENT, KNEE/ or OSTEOARTHRITIS, KNEE/
11. 9 or 10
12. injuries.mp. or exp "Wounds and Injuries"/
13. sports injuries.mp. or exp Athletic Injuries/
14. Cartilage/ or Cartilage, Articular/ or hyaline cartilage.mp. or Hyalin/ or Chondrocytes/
15. chondrocyte$.tw.
16. 12 or 13 or 14 or 15
17. exp Arthroplasty, Replacement, Knee/
18. knee replacement$.tw.
19. exp TRANSPLANTATION/
20. transplantation$.tw.
21. arthroplasty.mp. or exp ARTHROPLASTY/
22. debridement.mp. or exp DEBRIDEMENT/
23. Transplantation, Autologous/ or autologous cartilage transplantation.mp.
24. autologous cartilage implantation.tw.
25. MACI.tw.
26. drilling.tw.
27. microfracture.tw.
28. mosaicplasty.tw.
29. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30. 8 and 11 and 16 and 29

## EMBASE

### 2000–2004, updated weekly using Autoalert

1. exp Cartilage Cell/
2. exp Autotransplantation/
3. (chondrocyte$ and transplant$).mp.
4. (chondrocyte$ and implant$).mp.
5. exp Cell Transplantation/
6. exp CARTILAGE TRANSPLANTATION/ or exp CARTILAGE GRAFT/
7. autologous chondrocyte transplantation.mp.
8. autologous chondrocyte implantation.mp.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. exp KNEE ARTHRITIS/ or exp KNEE ARTHROSCOPY/ or exp KNEE SURGERY/ or exp KNEE OSTEOARTHRITIS/ or exp KNEE INJURY/ or exp KNEE DISEASE/ or exp KNEE/ or exp KNEE PAIN/ or exp KNEE INSTABILITY/
11. exp Cartilage Degeneration/
12. exp Articular Cartilage/
13. exp CHONDROPATHY/
14. exp Cartilage Cell/
15. exp Sport Injury/
16. exp Patella Fracture/
17. exp PATELLA/ or exp PATELLA CHONDROMALACIA/
18. exp KNEE OSTEOARTHRITIS/ or exp OSTEOARTHRITIS/
19. exp OSTEOCHONDRITIS DISSECANS/ or exp OSTEOCHONDRITIS/
20. exp KNEE/
21. KNEE/
22. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23. 9 and 22
24. limit 23 to yr=2000-2004
25. controlled-study.sh.
26. crossover-procedure.sh.
27. double-blind-procedure.sh.
28. phase-3-clinical-trial.sh.
29. placebo$.tw.
30. randomized-controlled-trial.sh.
31. single-blind-procedure.sh.
32. blind$.tw.
33. comparative study.tw.
34. (control$ adj1 trial$).tw.
35. cross?over$.tw.
36. factorial$.tw.
37. random$.tw.
38. 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37
39. human.sh.
40. nonhuman.sh.
41. 39 and 40
42. 40 not 41
43. 38 not 42
44. 24 and 43

1. mosaicplasty.mp.
2. (osteochondral and transplantation).mp.
3. autologous osteochondral transplantation.mp.
4. 1 or 2 or 3
5. exp KNEE ARTHRITIS/ or exp KNEE ARTHROSCOPY/ or exp KNEE SURGERY/ or exp KNEE OSTEOARTHRITIS/ or exp KNEE INJURY/ or exp KNEE DISEASE/ or exp KNEE/
6. 4 and 5
7. controlled-study.sh.
8. crossover-procedure.sh.
9. double-blind-procedure.sh.

10. phase-3-clinical-trial.sh.
11. placebo$.tw.
12. randomized-controlled-trial.sh.
13. single-blind-procedure.sh.
14. blind$.tw.
15. comparative study.tw.
16. (control$ adj1 trial$).tw.
17. cross?over$.tw.
18. factorial$.tw.
19. random$.tw.
20. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. human.sh.
22. nonhuman.sh.
23. 21 and 22
24. 22 not 23
25. 20 not 24
26. 6 and 25

## EMBASE

### 1996–2004

1. quality of life.mp. or exp "Quality of Life"/
2. quality adjusted life year.mp. or exp Quality Adjusted Life Year/
3. Qaly.tw.
4. health utility.mp.
5. EuroQol.tw.
6. SF-36.tw.
7. Rosser.tw.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. knee$.tw.
10. exp KNEE ARTHROGRAPHY/ or exp KNEE PAIN/ or exp KNEE/ or exp KNEE ARTHROPLASTY/ or exp KNEE OSTEOARTHRITIS/ or exp KNEE INSTABILITY/ or exp KNEE INJURY/ or exp KNEE ARTHROSCOPY/ or exp KNEE SURGERY/ or exp KNEE DISEASE/ or exp KNEE FUNCTION/ or exp KNEE ARTHRITIS/
11. 9 or 10
12. exp KNEE INJURY/ or exp SPORT INJURY/
13. injur$.tw.
14. exp hyalin/ or exp cartilage/ or exp hyaline cartilage/ or hyaline cartilage.mp. or exp cartilage degeneration/ or exp articular cartilage/
15. exp Cartilage Cell/
16. chondrocyte$.tw.
17. chondropathy.mp. or exp CHONDROPATHY/
18. exp Cartilage Degeneration/
19. 12 or 13 or 14 or 15 or 16 or 17 or 18
20. knee replacement$.tw.
21. knee arthroplasty.mp. or exp Knee Arthroplasty/
22. exp Total Knee Replacement/
23. cartilage transplantation.mp. or exp Cartilage Transplantation/
24. exp TRANSPLANTATION/ or transplantation.mp.
25. exp IMPLANTATION/
26. arthroplasty.mp. or exp ARTHROPLASTY/
27. debridement.mp. or exp DEBRIDEMENT/
28. autologous cartilage transplantation.mp. or cartilage transplantation/
29. autologous cartilage implantation.tw.
30. MACI.tw.
31. drilling.tw.
32. microfracture.tw.
33. mosaicplasty.tw.
34. 20 or 21 or 22 or 23 or 24 or 25 or 27 or 30 or 31 or 32 or 33
35. 8 and 11 and 19 and 34

## EMBASE

### 1996–2004

1. ECONOMICS/
2. "Costs and Cost Analysis"/
3. Cost Allocation/
4. Cost-Benefit Analysis/
5. Cost Control/
6. Cost Savings/
7. Cost of Illness/
8. Cost Sharing/
9. "Deductibles and Coinsurance"/
10. Medical Savings Accounts/
11. Health Care Costs/
12. Direct Service Costs/
13. Drug Costs/
14. Employer Health Costs/
15. Hospital Costs/
16. Health Expenditures/
17. Capital Expenditures/
18. Value of Life/
19. exp Economics, Hospital/
20. exp Economics, Medical/
21. Economics, Nursing/
22. Economics, Pharmaceutical/
23. exp "Fees and Charges"/
24. exp BUDGETS/
25. (low adj cost).mp.
26. (high adj cost).mp.
27. (health?care adj cost$).mp.
28. (fiscal or funding or financial or finance).tw.
29. (cost adj estimate$).mp.
30. (cost adj variable).mp.
31. (unit adj cost$).mp.
32. (economic$ or pharmacoeconomic$ or price$ or pricing).tw.
33. or/1-32

34. (cartilage and knee$).mp.
35. 33 and 34

## EMBASE

### 1996–2004

1. economic$.mp. or ECONOMICS/
2. cost$.mp. or exp "Costs and Cost Analysis"/
3. (resource$ or expenditure or burden).mp.
4. 1 or 2 or 3
5. exp CARTILAGE/or exp ARTICULAR CARTILAGE/or cartilage.mp or exp/CARTILAGE TRANSPLANTATION
6. knee.mp or exp KNEE/or exp KNEE SURGERY/or exp KNEE DISEASE/or exp KNEE OSTEOARTHRITIS/or exp KNEE INJURY/or exp KNEE ARTHRITIS
7. 4 and 5 and 6

## EMBASE

### 1980–2004

1. quality of life.mp. or exp "Quality of Life"/
2. quality adjusted life year.mp. or exp Quality Adjusted Life Year/
3. Qaly.tw.
4. health utility.mp.
5. EuroQol.tw.
6. SF-36.tw.
7. Rosser.tw.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. knee$.tw.
10. exp KNEE ARTHROGRAPHY/ or exp KNEE PAIN/ or exp KNEE/ or exp KNEE ARTHROPLASTY/ or exp KNEE OSTEOARTHRITIS/ or exp KNEE INSTABILITY/ or exp KNEE INJURY/ or exp KNEE ARTHROSCOPY/ or exp KNEE SURGERY/ or exp KNEE DISEASE/ or exp KNEE FUNCTION/ or exp KNEE ARTHRITIS/
11. 9 or 10
12. exp KNEE INJURY/ or exp SPORT INJURY/
13. injur$.tw.
14. exp hyalin/ or exp cartilage/ or exp hyaline cartilage/ or hyaline cartilage.mp. or exp cartilage degeneration/ or exp articular cartilage/
15. exp Cartilage Cell/
16. chondrocyte$.tw.
17. chondropathy.mp. or exp CHONDROPATHY/
18. exp Cartilage Degeneration/
19. 12 or 13 or 14 or 15 or 16 or 17 or 18
20. knee replacement$.tw.
21. knee arthroplasty.mp. or exp Knee Arthroplasty/
22. exp Total Knee Replacement/
23. cartilage transplantation.mp. or exp Cartilage Transplantation/
24. exp TRANSPLANTATION/ or transplantation.mp.
25. exp IMPLANTATION/
26. arthroplasty.mp. or exp ARTHROPLASTY/
27. debridement.mp. or exp DEBRIDEMENT/
28. autologous cartilage transplantation.mp. or cartilage transplantation/
29. autologous cartilage implantation.tw.
30. MACI.tw.
31. drilling.tw.
32. microfracture.tw.
33. mosaicplasty.tw.
34. 20 or 21 or 22 or 23 or 24 or 25 or 27 or 30 or 31 or 32 or 33
35. 8 and 11 and 19 and 34

## Sports Discus

### 2000–2004

1. exp knee/ or exp patella/ or patellofemoral pain syndrome/ or exp rotule/ or exp knee joint/
2. exp cartilage/ or exp articular cartilage/ or exp cartilage articulaire/ or exp cartilage semilunaire/ or exp chondrocyte/ or exp semilunar cartilage/ or exp cartilage disease/
3. exp CELL/
4. 1 or 2 or 3
5. autologous.mp.
6. (transplant$ and chondrocyte).mp.
7. (implant$ and chondrocyte).mp.
8. 5 or 6 or 7
9. 4 and 8

Note: mp=title, abstract, name of substance, MeSH subject heading

## The Cochrane Library (including CENTRAL and NEED)

### Issue 2 2004

"cartilage and knee*"
"chondrocyte* and knee*"

## NHS CRD databases

### May 2004

"knee"

## BIOSIS

**2000 to present (6 June 2004)**
"cartilage" and "transplantation" and "knee$"
"cartilage" and implantation" and "knee$"
autologous chondrocyte transplantation

## EBSCO Biomedical Reference Collection

**6 June 2004**
"chondrocyte*" and "transplantation*" and "knee*"
"cartilage" and "knee*"

## HStat

**6 June 2004**
"autologous" and chondrocyte*"
"cartilage" and "knee*"

## Medical Research Council (www.controlled-trials.com)

**June 2004**

## National Research Register

**6 June 2004**
"cartilage" and "knee*"
"chondrocyte*"

## ReFeR (Department of Health Research Findings Register)

**6 June 2004**
"chondrocyte*"
"cartilage and knee*"

## Science Citation Index and Social Sciences Citation Index

**6 June 2004**
"chondrocyte*" and (transplant* and implant*) and (knee* or cartilage* or patella*)

## American Academy of Orthopedic Surgeons Annual Meeting Abstracts

**2000–2004**

## Broad Internet search using meta-search engine Dogpile

# Appendix 4

# Assumptions used in the economic analysis

## Success rates

Success is defined or described differently in the various studies, but there are two main aspects:

- Symptoms and activities: these are closely related, in that pain is one of the key factors inhibiting return to activities. Therefore, they can be combined or induced, e.g. a return to full sporting activity implies freedom from severe pain. For cost-effectiveness purposes, all of these aspects need to be summarised into a utility score for QALY estimation.
- Long-term success in terms of avoidance of both osteoarthritis and the need for later knee replacement: none of the studies is long enough to provide data on knee replacement, so assumptions have to be made. The first is that any treatment that gives 100% hyaline cartilage will prevent later osteoarthritis and knee replacement. The second is more difficult, and is about what proportion of those with repairs that result in fibrocartilage will develop osteoarthritis and need TKR. One natural history study[18] suggested that patients aged over 18 years with chondral damage are at increased risk of osteoarthrits at 9 years of follow-up. Six out of eight patients with untreated injuries had radiological joint narrowing at follow-up. Another study[17] reported that after 14 years injured knees were more at risk of progression to osteoarthritis than the opposite non-injured knees. A third study[19] of untreated chondral lesions found no radiological differences at 9 years; but 9 years is a not a long time in the life of a knee, and there may be more osteoarthritis with longer follow-up.

It was assumed that all injured knees with fibrocartilage will develop osteoarthritis over time.

## Second line procedures

The following assumptions were made.

- ACI may be followed by another ACI, since the first ACI may fail for technical reasons such as failure of anchoring of the graft, which is no bar to another ACI.
- Mosaicplasty cannot be followed by another mosaicplasty because of damage to donor areas, but can be followed by ACI.
- Microfracture could be followed by mosaicplasty if the area is small, or by ACI.

TKR lasts for 10–15 years. Future TKRs may last longer, but it was assumed that it is undesirable to have to replace the original TKR, because the procedure is more difficult and more costly, and hence if the patient's life expectancy exceeds the expected longevity of the knee prosthesis, TKR is undesirable.

Less extensive procedures such as unicompartmental knee replacement were not included because these are the subject of ongoing research. However, in practice the cost differences, at least of first operation, may not be great.

Not all patients with osteoarthritis will progress to TKR. Steadman and colleagues[72] noted that many of their 'failures' declined further surgery, presumably because their symptoms were not bad, or could be controlled with analgesics such as paracetamol. (Paracetamol is taken as the first line drug, based on the Bandolier review,[98] with older and hence cheap non-steroidal drugs as second line). So the base case assumes 50%, but a sensitivity analysis was performed with 100%, which will give the best possible case for any procedure that reduces later osteoarthritis. The 50% level may be too high.

## Success rates after each procedure

The longest follow-ups come from case series, from centres of excellence in each procedure:

- ACI 85% success (95% CI 76 to 94) (Peterson, 10 years)[70]
- Microfracture: 80% success (95% CI 71 to 89) (Steadman)[72]
- Mosaicplasty: 90% success (95% CI 88 to 92) (Hangody, mean 4 years).[73]

Débridement and lavage do not appear to be effective, so their outcomes should be similar to natural history studies, such as:

- 80% success (95% CI 73 to 87) (Shelbourne)[19]
- 75% (95% CI 59 to 91) (Messner).[17]

However, all these results are too short term if one is considering avoidance of future knee replacements. Another option is to make assumptions based on the proportions with fibrocartilage.

### ACI

Briggs reported fibrocartilage in 48%.[66] So, even some of the 85% clinical successes at 10 years may develop osteoarthritis later, about 44%. (However, the Briggs results were at 1 year, and there may be more hyaline cartilage at 2 years or later, because the graft takes time to mature.)

The following assumptions are made for the three groups (with rounding):

- successes, good quality of life/knee score, hyaline cartilage: 50%
- successes in terms of good quality of life/knee score, but fibrocartilage: 40%
- failures, fibrocartilage: 10%

Therefore, 50% of all ACIs will develop osteoarthritis later, so 25% or 50% will undergo TKR eventually.

### Microfracture

Steadman reported that 20% developed hyaline cartilage (although this involved some extrapolation from results in horses). So 80% have fibrocartilage which will lead to osteoarthritis in the long term.

The following assumptions are made:

- clinical successes with hyaline: 20%
- short-term clinical successes with fibrocartilage, which will later fail: 60%
- failures: 20%.

Hence, 40% or 80% are assumed to need TKR.

### Mosaicplasty

Few or none have complete hyaline because they have fibrocartilage among the transplanted cylinders. Therefore, of the 90% successes in the Hangody series,[73] all may go on to long-term osteoarthritis, so 50% or 100% of mosaicplasty patients eventually undergo TKR.

## Quality of life gains

Minas[77] gives a quality of life gain of 0.1, but gives no detail on how he obtains this from his SF-36 data. Indeed, the quality of life figure is not given in the paper in which he quotes a cost per QALY, but only in subsequent correspondence. There is a method for converting SF-36 data to QALYs,[99] but Mina does not cite this.

Expert opinion suggests a gain of 0.1.[81]

Studies of quality of life gains after TKR report gains of 0.06–0.1. There is an outlier reporting 0.2, using EQ-5D. Gains from procedures such as ACI in isolated chondral lesions are unlikely to give as great a gain as a TKR.

Knutsen[63] found no real quality of life difference between microfracture and ACI in the short term.

*[Confidential material removed]*

Therefore, options for modelling are:

- no significant quality of life difference between microfracture and ACI
- a gain of 0.1 after all procedures
- to use 0.2 as the most optimistic case

*[confidential material removed]*

- all quality of life gains should be discounted at 3.5%
- to assume that this group of patients incurs no further injuries (that is unlikely, and the Messner paper[17] notes that a fair proportion develop osteoarthritis in the other knee), and hence that effective treatment of the first injury provides a lifelong cure. This again provides an overoptimistic outcome.

## Costs

The costs of the various procedures were obtained from Aberdeen Royal Infirmary, but since not all procedures are carried out there (e.g. no mosaicplasty), and since costs may vary among hospitals, costs were also sought from Southampton General Hospital. Most costs were fairly similar, but there were a couple of exceptions, discussed below.

- First knee replacement £5417
- Second knee replacement £10,077
- Arthroscopy £552 (diagnostic) and £602 (lavage and débridement)

- ACI (arthroscopic) £3184 not including cells; £6384 including cells
- Microfracture £2348
- Mosaicplasty £3710 (estimate because not done in Aberdeen)

The cost differences were in arthroscopy, where the Southampton cost is £804, but this cost is also used for microfracture, and is presumably the average for a number of short arthroscopic procedures. The Aberdeen cost was used for basic diagnostic and débridement arthroscopy.

The biggest differences in cost between the two hospitals are in microfracture and mosaicplasty, and arise because Aberdeen assumes that they are inpatient procedures, whereas Southampton classes them as day-case procedures. In sensitivity analysis the Aberdeen cost for microfracture was halved. ACI is not done in Southampton at present.

Allowing for inflation, these costs are compatible with those used in the last review for NICE.

A discounting rate of 3.5% was used.

## Other assumptions

The mean age of patients being considered for ACI, etc., was 32 years.

# Appendix 5

# Modelling results

## Short-term modelling results: ICERs relative to no further treatment

| **Common QoL increment of 0.1** | **Year 1** | **Year 2** | **Year 5** | **Year 10** |
|---|---|---|---|---|
| ACI open knee | £86,460 | £43,974 | £18,502 | £10,045 |
| ACI arthroscopic | £63,840 | £32,469 | £13,661 | £7,417 |
| Mosaicplasty | £37,100 | £18,869 | £7,939 | £4,310 |
| Microfracture | £23,480 | £11,942 | £5,025 | £2,728 |
| **Different QoL increment** | **Year 1** | **Year 2** | **Year 5** | **Year 10** |
| Mosaicplasty (0.05) | £74,200 | £37,738 | £15,878 | £8,620 |
| ACI open knee (0.20) | £43,230 | £21,987 | £9,251 | £5,022 |
| ACI arthroscopic (0.20) | £31,920 | £16,234 | £6,831 | £3,708 |
| Microfracture (0.10) | £23,480 | £11,942 | £5,025 | £2,728 |

## Medium-term modelling results: ICERs relative to no further treatment

| **Different QoL increment**<br>**10-year success % applied to all years** | **Year 1** | **Year 2** | **Year 5** | **Year 10** |
|---|---|---|---|---|
| Mosaicplasty (0.05) | £84,318 | £42,884 | £18,043 | £9,796 |
| ACI open knee (0.20) | £51,464 | £26,175 | £11,013 | £5,979 |
| ACI arthroscopic (0.20) | £38,000 | £19,327 | £8,132 | £4,415 |
| Microfracture (0.10) | £29,350 | £14,927 | £6,281 | £3,410 |

## Long-term modelling results

### First line treatments, no second line

***Base case***

| **Among 100 Cohort** | **Débridement** | **ACI** | **Microfracture** | **Mosaicplasty** |
|---|---|---|---|---|
| QALYs (non-disc) | 3465.8 | 3775.4 | 3646.5 | 3582.1 |
| **QALYs (disc)** | **1785.9** | **1957.6** | **1901.2** | **1881.3** |
| 1st line cost | £0 | £638,400 | £234,800 | £371,000 |
| TKA costs (disc) | £666,025 | £333,013 | £532,820 | £666,025 |
| **Total costs (disc)** | **£666,025** | **£971,413** | **£767,620** | **£1,037,025** |
| 1st TKRs (non-disc)[a] | 98.3 | 49.1 | 78.6 | 98.3 |
| 2nd TKRs (non-disc)[b] | 90.7 | 45.4 | 72.6 | 90.7 |
| | 100% of those offered accepting TKR | | | |

| **Cost-effectiveness** | **Cost** | **QALYs** | **ICER** |
|---|---|---|---|
| Débridement | £666,025 | 1785.9 | – |
| Microfracture | £767,620 | 1901.2 | **£881** |
| ACI | £971,413 | 1957.6 | **£3,617** |
| Mosaicplasty | £1,037,025 | 1881.3 | **Dominated** |

*continued*

| Among 100 cohort | Débridement | ACI | Microfracture | Mosaicplasty |
|---|---|---|---|---|
| QALYs (non-disc) | 3416.0 | 3750.5 | 3606.7 | 3532.4 |
| **QALYs (disc)** | **1769.6** | **1949.4** | **1888.1** | **1865.0** |
| 1st line cost | £0 | £638,400 | £234,800 | £371,000 |
| TKA costs (disc) | £248,731 | £124,365 | £198,985 | £248,731 |
| **Total costs (disc)** | **£248,731** | **£762,765** | **£433,785** | **£619,731** |
| 1st TKRs (non-disc) | 49.1 | 24.6 | 39.3 | 49.1 |
| 2nd TKRs (non-disc) | 22.7 | 11.3 | 18.1 | 22.7 |
| | 50% of those offered accepting TKR | | | |
| **Cost-effectiveness** | **Cost** | **QALYs** | **ICER** | |
| Débridement | £248,731 | 1769.6 | – | |
| Microfracture | £433,785 | 1888.1 | **£1,561** | |
| Mosaicplasty | £619,731 | 1865.0 | **Dominated** | |
| ACI | £762,765 | 1949.4 | **£5,372** | |

[a] The number of patients within the cohort who undergo a first TKR. This has not been discounted. As the cohort is 100, these can also be seen as the percentage of patients who will be offered and accept a first TKR.
[b] As in the above, only being the undiscounted number of patients who are offered and accept a second, replacement TKR, i.e. a replacement in the same leg.
disc, discounted.

***Time to TKA lengthened from 15 to 20 years***

| Among 100 cohort | Débridement | ACI | Microfracture | Mosaicplasty |
|---|---|---|---|---|
| QALYs (non-disc) | 3479.1 | 3801.7 | 3686.5 | 3639.5 |
| **QALYs (disc)** | **1794.9** | **1973.8** | **1926.0** | **1916.7** |
| 1st line cost | £0 | £638,400 | £234,800 | £371,000 |
| TKA costs (disc) | £478,612 | £239,306 | £382,889 | £478,612 |
| **Total costs (disc)** | **£478,612** | **£877,706** | **£617,689** | **£849,612** |
| 1st TKRs (non-disc) | 96.9 | 48.5 | 77.5 | 96.9 |
| 2nd TKRs (non-disc) | 78.0 | 39.0 | 62.4 | 78.0 |
| | 100% of those offered accepting TKR | | | |
| **Cost-effectiveness** | **Cost** | **QALYs** | **ICER** | |
| Débridement | £478,612 | 1794.9 | – | |
| Microfracture | £617,689 | 1926.0 | **£1,061** | |
| Mosaicplasty | £849,612 | 1916.7 | **Dominated** | |
| ACI | £877,706 | 1973.8 | **£5,443** | |
| **Among 100 cohort** | **Débridement** | **ACI** | **Microfracture** | **Mosaicplasty** |
| QALYs (non-disc) | 3444.8 | 3784.5 | 3659.1 | 3605.2 |
| **QALYs (disc)** | **1783.9** | **1968.3** | **1917.2** | **1905.7** |
| 1st line cost | £0 | £638,400 | £234,800 | £371,000 |
| TKA costs (disc) | £187,928 | £93,964 | £150,342 | £187,928 |
| **Total costs (disc)** | **£187,928** | **£732,364** | **£385,142** | **£558,928** |
| 1st TKRs (non-disc) | 48.5 | 24.2 | 38.8 | 48.5 |
| 2nd TKRs (non-disc) | 19.5 | 9.8 | 15.6 | 19.5 |
| | 50% of those offered accepting TKR | | | |
| **Cost-effectiveness** | **Cost** | **QALYs** | **ICER** | |
| Débridement | £187,928 | 1783.9 | – | |
| Microfracture | £385,142 | 1917.2 | **£1,480** | |
| Mosaicplasty | £558,928 | 1905.7 | **Dominated** | |
| ACI | £732,364 | 1968.3 | **£6,799** | |

## Quality of life gains

### *Quality of life among those being offered TKR*

There are no data on the quality of life of those being offered TKR relative to that of those receiving the treatments under consideration for chondral lesions. These latter, assumed to have a pre-operative quality of life of 0.6, are assumed to have no quality of life increment if the treatment is a failure, but a 0.1 quality of life increment if the treatment is a success.

Introspection suggests that the quality of life gain from TKR may be higher than this. The sensitivity analyses below reduce the pre-TKR quality of life to 0.6 among those accepting it, a gain of 0.2 being recorded among those surviving the procedure. In the analysis of 50% rejecting TKR, these are again placed midway in terms of quality of life at 0.7.

| **Among 100 cohort** | **Débridement** | **ACI** | **Microfracture** | **Mosaicplasty** |
|---|---|---|---|---|
| QALYs (non-disc) | 3427.9 | 3756.5 | 3616.2 | 3544.2 |
| **QALYs (disc)** | **1766.6** | **1947.9** | **1885.7** | **1862.0** |
| 1st line cost | £0 | £638,400 | £234,800 | £371,000 |
| TKA costs (disc) | £666,025 | £333,013 | £532,820 | £666,025 |
| **Total costs (disc)** | **£666,025** | **£971,413** | **£767,620** | **£1,037,025** |
| 1st TKRs (non-disc) | 98.3 | 49.1 | 78.6 | 98.3 |
| 2nd TKRs (non-disc) | 90.7 | 45.4 | 72.6 | 90.7 |
| | 100% of those offered accepting TKR | | | |
| **Cost-effectiveness** | **Cost** | **QALYs** | **ICER** | |
| Débridement | £666,025 | 1766.6 | – | |
| Microfracture | £767,620 | 1885.7 | **£853** | |
| ACI | £971,413 | 1947.9 | **£3280** | |
| Mosaicplasty | £1,037,025 | 1862.0 | **Dominated** | |
| **Among 100 Cohort** | **Débridement** | **ACI** | **Microfracture** | **Mosaicplasty** |
| QALYs (non-disc) | 3302.1 | 3693.6 | 3515.6 | 3418.4 |
| **QALYs (disc)** | **1725.3** | **1927.3** | **1852.7** | **1820.7** |
| 1st line cost | £0 | £638,400 | £234,800 | £371,000 |
| TKA costs (disc) | £248,731 | £124,365 | £198,985 | £248,731 |
| **Total costs (disc)** | **£248,731** | **£762,765** | **£433,785** | **£619,731** |
| 1st TKRs (non-disc) | 49.1 | 24.6 | 39.3 | 49.1 |
| 2nd TKRs (non-disc) | 22.7 | 11.3 | 18.1 | 22.7 |
| | 50% of those offered accepting TKR | | | |
| **Cost-effectiveness** | **Cost** | **QALYs** | **ICER** | |
| Débridement | £248,731 | 1725.3 | – | |
| Microfracture | £433,785 | 1852.7 | **£1453** | |
| Mosaicplasty | £619,731 | 1820.7 | **Dominated** | |
| ACI | £762,765 | 1927.3 | **£4415** | |

Just as TKR may have a higher quality of life increment, a sensitivity analysis as regards the quality of life increment among first line treatment successes can be performed: from a base quality of life of 0.8, first line treatment successes can be assumed to gain 0.2 to attain a quality of life of 1.0. It seems unlikely that the quality of life gain from TKR will be less than that from first line treatments, and the assumptions of the previous sensitivity analysis are retained in the following four tables of results.

| **Among 100 cohort** | **Débridement** | **ACI** | **Microfracture** | **Mosaicplasty** |
|---|---|---|---|---|
| QALYs (non-disc) | 3427.9 | 4029.3 | 3782.2 | 3660.5 |
| **QALYs (disc)** | **1766.6** | **2103.9** | **1994.8** | **1957.4** |
| 1st line cost | £0 | £638,400 | £234,800 | £371,000 |
| TKA costs (disc) | £666,025 | £333,013 | £532,820 | £666,025 |
| **Total costs (disc)** | **£666,025** | **£971,413** | **£767,620** | **£1,037,025** |
| 1st TKRs (non-disc) | 98.3 | 49.1 | 78.6 | 98.3 |
| 2nd TKRs (non-disc) | 90.7 | 45.4 | 72.6 | 90.7 |
| | 100% of those offered accepting TKR | | | |
| **Cost-effectiveness** | **Cost** | **QALYs** | **ICER** | |
| Débridement | £666,025 | 1766.6 | – | |
| Microfracture | £767,620 | 1994.8 | **£445** | |
| ACI | £971,413 | 2103.9 | **£1868** | |
| Mosaicplasty | £1,037,025 | 1957.4 | **Dominated** | |
| **Among 100 cohort** | **Débridement** | **ACI** | **Microfracture** | **Mosaicplasty** |
| QALYs (non-disc) | 3302.1 | 3966.5 | 3681.6 | 3534.7 |
| **QALYs (disc)** | **1725.3** | **2083.2** | **1961.8** | **1916.1** |
| 1st line cost | £0 | £638,400 | £234,800 | £371,000 |
| TKA costs (disc) | £248,731 | £124,365 | £198,985 | £248,731 |
| **Total costs (disc)** | **£248,731** | **£762,765** | **£433,785** | **£619,731** |
| 1st TKRs (non-disc) | 49.1 | 24.6 | 39.3 | 49.1 |
| 2nd TKRs (non-disc) | 22.7 | 11.3 | 18.1 | 22.7 |
| | 50% of those offered accepting TKR | | | |
| **Cost-effectiveness** | **Cost** | **QALYs** | **ICER** | |
| Débridement | £248,731 | 1725.3 | – | |
| Microfracture | £433,785 | 1961.8 | **£783** | |
| Mosaicplasty | £619,731 | 1916.1 | **Dominated** | |
| ACI | £762,765 | 2083.2 | **£2709** | |

## Discount rates

When the tenth wave of TARs was commissioned current NICE guidance was to use a discount rate of 1.5% for health effects and 6.0% for financial effects. Applying these percentages to the base-case assumptions gives the following results.

| **Among 100 cohort** | **Débridement** | **ACI** | **Microfracture** | **Mosaicplasty** |
|---|---|---|---|---|
| QALYs (non-disc) | 3465.8 | 3775.4 | 3646.5 | 3582.1 |
| **QALYs (disc)** | **2533.7** | **2767.5** | **2679.3** | **2640.2** |
| 1st line cost | £0 | £638,400 | £234,800 | £371,000 |
| TKA costs (disc) | £404,205 | £202,103 | £323,364 | £404,205 |
| **Total costs (disc)** | **£404,205** | **£840,503** | **£558,164** | **£775,205** |
| 1st TKRs (non-disc) | 98.3 | 49.1 | 78.6 | 98.3 |
| 2nd TKRs (non-disc) | 90.7 | 45.4 | 72.6 | 90.7 |
| | 100% of those offered accepting TKR | | | |

*continued*

| **Cost-effectiveness** | **Cost** | **QALYs** | **ICER** | |
|---|---|---|---|---|
| Débridement | £404,205 | 2533.7 | – | |
| Microfracture | £558,164 | 2679.3 | **£1057** | |
| Mosaicplasty | £775,205 | 2640.2 | **Dominated** | |
| ACI | £840,503 | 2767.5 | **£3200** | |
| **Among 100 cohort** | **Débridement** | **ACI** | **Microfracture** | **Mosaicplasty** |
| QALYs (non-disc) | 3416.0 | 3750.5 | 3606.7 | 3532.4 |
| **QALYs (disc)** | **2503.3** | **2752.3** | **2655.0** | **2609.8** |
| 1st line cost | £0 | £638,400 | £234,800 | £371,000 |
| TKA costs (disc) | £159,920 | £79,960 | £127,936 | £159,920 |
| **Total costs (disc)** | **£159,920** | **£718,360** | **£362,736** | **£530,920** |
| 1st TKRs (non-disc) | 49.1 | 24.6 | 39.3 | 49.1 |
| 2nd TKRs (non-disc) | 22.7 | 11.3 | 18.1 | 22.7 |
| | 50% of those offered accepting TKR | | | |
| **Cost-effectiveness** | **Cost** | **QALYs** | **ICER** | |
| Débridement | £159,920 | 2503.3 | – | |
| Microfracture | £362,736 | 2655.0 | **£1337** | |
| Mosaicplasty | £530,920 | 2609.8 | **Dominated** | |
| ACI | £718,360 | 2752.3 | **£3654** | |

## Knutsen biopsy data

Knutsen and colleagues[63] present biopsy results for ACI and microfracture, their respective success rates being 95% and 97.5%.

| | **Hyaline** | **Mixed** | **Fibrocartilage** | **Unknown/no repair** |
|---|---|---|---|---|
| ACI | 6 | 10 | 11 | 5 |
| Microfracture | 4 | 6 | 18 | 7 |

The grouping of biopsies that are unknown owing to an unclear biopsy and those that show no repair is unhelpful, but given the reported failure rates of 5% and 2.5%, it appears unlikely that the microfracture unknown/no repair group was significantly biased towards no repair compared with the ACI group. As a consequence, the unknown/no repair group is ignored in the sensitivity analyses that follow.

- Hyaline cartilage prevents TKR.
- Mixed cartilage results in TKR being offered.
- Fibrocartilage results in TKR being offered.

| **Among 100 cohort** | **Débridement** | **ACI** | **Microfracture** |
|---|---|---|---|
| QALYs (non-disc) | 3465.8 | 3670.2 | 3645.6 |
| **QALYs (disc)** | **1785.9** | **1918.8** | **1910.5** |
| 1st line cost | £0 | £638,400 | £234,800 |
| TKA costs (disc) | £666,025 | £525,420 | £573,258 |
| **Total costs (disc)** | **£666,025** | **£1,163,820** | **£808,058** |
| 1st TKRs (non-disc) | 98.3 | 77.5 | 84.6 |
| 2nd TKRs (non-disc) | 90.7 | 71.6 | 78.1 |
| | 100% of those offered accepting TKR | | |

*continued*

| Cost-effectiveness | Cost | QALYs | ICER |
|---|---|---|---|
| Débridement | £666,025 | 1785.9 | – |
| Microfracture | £808,058 | 1910.5 | **£1,140** |
| Mosaicplasty | £1,037,025 | 1881.3 | **Dominated** |
| ACI | £1,163,820 | 1918.8 | **£42,858** |
| **Among 100 Cohort** | **Débridement** | **ACI** | **Microfracture** |
| QALYs (non-disc) | 3416.0 | 3630.9 | 3602.8 |
| **QALYs (disc)** | **1769.6** | **1905.9** | **1896.4** |
| 1st line cost | £0 | £638,400 | £234,800 |
| TKA costs (disc) | £248,731 | £196,221 | £214,086 |
| **Total costs (disc)** | **£248,731** | **£834,621** | **£448,886** |
| 1st TKRs (non-disc) | 49.1 | 38.8 | 42.3 |
| 2nd TKRs (non-disc) | 22.7 | 17.9 | 19.5 |
| | 50% of those offered accepting TKR | | |
| **Cost-effectiveness** | **Cost** | **QALYs** | **ICER** |
| Débridement | £248,731 | 1769.6 | – |
| Microfracture | £448,886 | 1896.4 | **£1,578** |
| Mosaicplasty | £619,731 | 1865.0 | **Dominated** |
| ACI | £834,621 | 1905.9 | **£40,708** |

- Hyaline cartilage prevents TKR.
- Mixed cartilage prevents TKR.
- Fibrocartilage results in TKR being offered.

| Among 100 cohort | Débridement | ACI | Microfracture |
|---|---|---|---|
| QALYs (non-disc) | 3465.8 | 3806.2 | 3726.4 |
| **QALYs (disc)** | **1785.9** | **1972.5** | **1942.4** |
| 1st line cost | £0 | £638,400 | £234,800 |
| TKA costs (disc) | £666,025 | £291,078 | £434,106 |
| **Total costs (disc)** | **£666,025** | **£929,478** | **£668,906** |
| 1st TKRs (non-disc) | 98.3 | 43.0 | 64.1 |
| 2nd TKRs (non-disc) | 90.7 | 39.7 | 59.1 |
| | 100% of those offered accepting TKR | | |
| **Cost-effectiveness** | **Cost** | **QALYs** | **ICER** |
| Débridement | £666,025 | 1785.9 | – |
| Microfracture | £668,906 | 1942.4 | **£18** |
| ACI | £929,478 | 1972.5 | **£8,659** |
| **Among 100 cohort** | **Débridement** | **ACI** | **Microfracture** |
| QALYs (non-disc) | 3416.0 | 3784.5 | 3694.0 |
| **QALYs (disc)** | **1769.6** | **1965.3** | **1931.7** |
| 1st line cost | £0 | £638,400 | £234,800 |
| TKA costs (disc) | £248,731 | £108,705 | £162,119 |
| **Total costs (disc)** | **£248,731** | **£747,105** | **£396,919** |
| 1st TKRs (non-disc) | 49.1 | 21.5 | 32.0 |
| 2nd TKRs (non-disc) | 22.7 | 9.9 | 14.8 |
| | 50% of those offered accepting TKR | | |

*continued*

| Cost-effectiveness | Cost | QALYs | ICER |
|---|---|---|---|
| Débridement | £248,731 | 1769.6 | – |
| Microfracture | £396,919 | 1931.7 | **£914** |
| ACI | £747,105 | 1965.3 | **£10,421** |

## With first and second line treatments

***Base-case assumptions and equal treatment effectiveness first and second line***

| Mosaicplasty (MOS) | Débridement | MOS | MOS–MFX | MOS–ACI |
|---|---|---|---|---|
| QALYs (non-disc) | 3465.8 | 3582.1 | 3599.9 | 3612.2 |
| **QALYs (disc)** | **1785.9** | **1881.3** | **1892.2** | **1897.3** |
| 1st line cost | £0 | £371,000 | £371,000 | £371,000 |
| Arthroscopy costs | | | £5,520 | £5,520 |
| 2nd line cost | | | £21,919 | £59,595 |
| TKA costs (disc) | £666,025 | £666,025 | £649,593 | £630,650 |
| **Total costs (disc)** | **£666,025** | **£1,037,025** | **£1,048,032** | **£1,066,765** |
| 1st TKRs (non-disc) | 98.3 | 98.3 | 96.3 | 93.3 |
| 2nd TKRs (non-disc) | 90.7 | 90.7 | 88.8 | 86.1 |
| | 100% of those offered accepting TKR | | | |

| | Cost | QALYs | ICER |
|---|---|---|---|
| Débridement | £666,025 | 1785.9 | – |
| MOS | £1,037,025 | 1881.3 | **£3,889** |
| MOS 1st line, MFX 2nd line | £1,048,032 | 1892.2 | **£1,012** |
| MOS 1st line, ACI 2nd line | £1,066,765 | 1897.3 | **£3,650** |

| Microfracture (MFX) | Débridement | MFX | MFX–ACI | MFX–MOS |
|---|---|---|---|---|
| QALYs (non-disc) | 3465.8 | 3646.5 | 3706.7 | 3670.3 |
| **QALYs (disc)** | **1785.9** | **1901.2** | **1933.2** | **1919.5** |
| 1st line cost | £0 | £234,800 | £234,800 | £234,800 |
| Arthroscopy costs | | | £11,040 | £11,040 |
| 2nd line cost | | | £119,191 | £69,266 |
| TKA costs (disc) | £666,025 | £532,820 | £462,069 | £523,485 |
| **Total costs (disc)** | **£666,025** | **£767,620** | **£827,100** | **£838,592** |
| 1st TKRs (non-disc) | 98.3 | 78.6 | 68.8 | 78.5 |
| 2nd TKRs (non-disc) | 90.7 | 72.6 | 63.4 | 72.3 |
| | 100% of those offered accepting TKR | | | |

| | Cost | QALYs | ICER |
|---|---|---|---|
| Débridement | £666,025 | 1785.9 | – |
| MFX | £767,620 | 1901.2 | **£881** |
| MFX 1st line, ACI 2nd line | £827,100 | 1933.2 | **£1858** |
| MFX 1st line, MOS 2nd line | £838,592 | 1919.5 | **Dominated** |

*continued*

| ACI | Débridement | ACI | ACI–MFX | ACI–MOS | ACI–ACI |
|---|---|---|---|---|---|
| QALYs (non-disc) | 3465.8 | 3775.4 | 3793.3 | 3787.3 | 3805.5 |
| **QALYs (disc)** | **1785.9** | **1957.6** | **1968.4** | **1966.7** | **1973.6** |
| 1st line cost | £0 | £638,400 | £638,400 | £638,400 | £638,400 |
| Arthroscopy costs | £0 | £0 | £5,520 | £5,520 | £5,520 |
| 2nd line cost | £0 | £0 | £21,919 | £34,633 | £59,595 |
| TKA costs (disc) | £666,025 | £333,013 | £316,581 | £328,345 | £297,637 |
| **Total costs (disc)** | **£666,025** | **£971,413** | **£982,419** | **£1,006,898** | **£1,001,152** |
| 1st TKRs (non-disc) | 98.3 | 49.1 | 47.1 | 49.1 | 44.2 |
| 2nd TKRs (non-disc) | 90.7 | 45.4 | 43.4 | 45.2 | 40.8 |
| | 100% of those offered accepting TKR | | | | |

| | Cost | QALYs | ICER |
|---|---|---|---|
| Débridement | £666,025 | 1785.9 | – |
| ACI | £971,413 | 1957.6 | **£1,779** |
| ACI 1st line, MFX 2nd line | £982,419 | 1968.4 | **£1,012** |
| ACI 1st line, ACI 2nd line | £1,001,152 | 1973.6 | **£3,650** |
| ACI 1st line, MOS 2nd line | £1,006,898 | 1966.7 | **Dominated** |

| Most cost-effective treatment within groups | | Cost | QALY | |
|---|---|---|---|---|
| Débridement | Débridement | £666,025 | 1,786 | |
| MFX | MFX 1st line, ACI 2nd line | £827,100 | 1,933 | |
| MOS | MOS 1st line, ACI 2nd line | £1,066,765 | 1,897 | |
| ACI | ACI 1st line, ACI 2nd line | £1,001,152 | 1,974 | |
| | At £20,000 per QALY threshold | | | |
| **Ordered by cost** | | **Cost** | **QALY** | **£ per QALY** |
| | Débridement | £666,025 | 1,786 | – |
| | MFX 1st line, ACI 2nd line | £827,100 | 1,933 | **£1,094** |
| | ACI 1st line, ACI 2nd line | £1,001,152 | 1,974 | **£4,315** |
| | MOS 1st line, ACI 2nd line | £1,066,765 | 1,897 | **Dominated** |

| **Mosaicplasty** | **Débridement** | **MOS** | **MOS–MFX** | **MOS–ACI** |
|---|---|---|---|---|
| QALYs (non-disc) | 3416.0 | 3532.4 | 3551.5 | 3565.1 |
| **QALYs (disc)** | **1769.6** | **1865.0** | **1876.3** | **1881.9** |
| 1st line cost | £0 | £371,000 | £371,000 | £371,000 |
| Arthroscopy costs | | | £5,520 | £5,520 |
| 2nd line cost | | | £21,919 | £59,595 |
| TKA costs (disc) | £248,731 | £248,731 | £242,628 | £235,542 |
| **Total costs (disc)** | **£248,731** | **£619,731** | **£641,067** | **£671,658** |
| 1st TKRs (non-disc) | 49.1 | 49.1 | 48.1 | 46.7 |
| 2nd TKRs (non-disc) | 22.7 | 22.7 | 22.2 | 21.5 |
| | 50% of those offered accepting TKR | | | |
| | **Cost** | **QALYs** | **ICER** | |
| Débridement | £248,731 | 1769.6 | – | |
| MOS | £619,731 | 1865.0 | **£3,889** | |
| MOS 1st line, MFX 2nd line | £641,067 | 1876.3 | **£1,882** | |
| MOS 1st line, ACI 2nd line | £671,658 | 1881.9 | **£5,485** | |
| **Microfracture** | **Débridement** | **MFX** | **MFX–ACI** | **MFX–MOS** |
| QALYs (non-disc) | 3416.0 | 3606.7 | 3674.1 | 3631.5 |
| **QALYs (disc)** | **1769.6** | **1888.1** | **1923.0** | **1906.8** |
| 1st line cost | £0 | £234,800 | £234,800 | £234,800 |
| Arthroscopy costs | | | £11,040 | £11,040 |
| 2nd line cost | | | £119,191 | £69,266 |
| TKA costs (disc) | £248,731 | £198,985 | £172,608 | £195,601 |
| **Total costs (disc)** | **£248,731** | **£433,785** | **£537,638** | **£510,707** |
| 1st TKRs (non-disc) | 49.1 | 39.3 | 34.4 | 39.3 |
| 2nd TKRs (non-disc) | 22.7 | 18.1 | 15.8 | 18.1 |
| | 50% of those offered accepting TKR | | | |
| | **Cost** | **QALYs** | **ICER** | |
| Débridement | £248,731 | 1769.6 | – | |
| MFX | £433,785 | 1888.1 | **£1,561** | |
| MFX 1st line, MOS 2nd line | £510,707 | 1906.8 | **£4,114** | |
| MFX 1st line, ACI 2nd line | £537,638 | 1923.0 | **£1,668** | |

| ACI | Débridement | ACI | ACI–MFX | ACI–MOS | ACI–ACI |
|---|---|---|---|---|---|
| QALYs (non-disc) | 3416.0 | 3750.5 | 3769.7 | 3762.9 | 3783.3 |
| **QALYs (disc)** | **1769.6** | **1949.4** | **1960.7** | **1958.7** | **1966.3** |
| 1st line cost | £0 | £638,400 | £638,400 | £638,400 | £638,400 |
| Arthroscopy costs | £0 | £0 | £5,520 | £5,520 | £5,520 |
| 2nd line cost | £0 | £0 | £21,919 | £34,633 | £59,595 |
| TKA costs (disc) | £248,731 | £124,365 | £118,263 | £122,674 | £111,176 |
| **Total costs (disc)** | **£248,731** | **£762,765** | **£784,102** | **£801,227** | **£814,692** |
| 1st TKRs (non-disc) | 49.1 | 24.6 | 23.6 | 24.5 | 22.1 |
| 2nd TKRs (non-disc) | 22.7 | 11.3 | 10.9 | 11.3 | 10.2 |
| | 50% of those offered accepting TKR | | | | |

| | Cost | QALYs | ICER |
|---|---|---|---|
| Débridement | £248,731 | 1769.6 | – |
| ACI | £762,765 | 1949.4 | **£2,859** |
| ACI 1st line, MFX 2nd line | £784,102 | 1960.7 | **£1,882** |
| ACI 1st line, MOS 2nd line | £801,227 | 1958.7 | **Dominated** |
| ACI 1st line, ACI 2nd line | £814,692 | 1966.3 | **£5,485** |

| Most cost-effective treatment within groups | | Cost | QALY |
|---|---|---|---|
| **Débridement** | Débridement | £248,731 | 1,770 |
| MFX | MFX 1st line, ACI 2nd line | £537,638 | 1,923 |
| MOS | MOS 1st line, ACI 2nd line | £671,658 | 1,882 |
| ACI | ACI 1st line, ACI 2nd line | £814,692 | 1,966 |
| | At £20,000 per QALY threshold | | |

| Ordered by cost | | Cost | QALY | £ per QALY |
|---|---|---|---|---|
| | Débridement | £248,731 | 1,770 | – |
| | MFX 1st line, ACI 2nd line | £537,638 | 1,923 | **£1,883** |
| | MOS 1st line, ACI 2nd line | £671,658 | 1,882 | **Dominated** |
| | ACI 1st line, ACI 2nd line | £814,692 | 1,966 | **£6,397** |

# Appendix 6

## Study characteristics

***TABLE 15*** *Patient characteristics*

| Study | *n* | Mean age (years) | Defect size ($cm^2$) | Aetiology | Defect site | Previous surgery |
|---|---|---|---|---|---|---|
| Bentley, 2003[64]<br>UK<br><br>ACI vs mosaicplasty<br><br>RCT<br><br>Follow-up: 1 year | 100 | 31.3 | 4.66 | **All patients (*n* = 100)**<br>Trauma: 46 (46%)<br>OCD: 19 (19%)<br>Chondromalacia patellae: 14 (14%)<br>Other: 21 (21%); reported as "probably post-traumatic"<br><br>**ACI (*n* = 58)**<br>Trauma: 24 (41%)<br>OCD: 14 (24%)<br>Chondromalacia patellae: 12 (21%)<br>Other: 8 (14%)<br><br>**Mosaicplasty (*n* = 42)**<br>Trauma: 22 (52%)<br>OCD: 5 (12%)<br>Chondromalacia patellae: 2 (5%)<br>Other: 13 (31%) | **All patients (*n* = 100)**<br>Median femoral condyle: 53 (53%)<br>Patella: 25 (25%)<br>Lateral femoral condyle: 18 (18%)<br>Trochlea: 3 (3%)<br>Lateral tibial condyle: 1 (1%)<br><br>**ACI (*n* = 58)**<br>Median femoral condyle: 24 (45%)<br>Patella: 20 (38%)<br>Lateral femoral condyle: 13 (25%)<br>Trochlea: 1 (2%)<br>Lateral tibial condyle: 0 (0%)<br><br>**Mosaicplasty (*n* = 42)**<br>Median femoral condyle: 29 (69%)<br>Patella: 5 (12%)<br>Lateral femoral condyle: 5 (12%)<br>Trochlea: 2 (5%)<br>Lateral tibial condyle: 1 (2%) | **Total *n* (%) with previous surgery: 94 (94%)**<br>No details |
| Horas, 2003[65]<br>Germany<br><br>ACI vs osteochondral transplantation<br><br>Quasi-RCT<br><br>Follow-up: 2 years | 40 | 33.4 | 3.75 | Trauma: 40 (100%) | Median femoral condyle: 33 (82.5%) (in one patient, the patellofemoral articulation was also affected)<br>Lateral femoral condyle: 7 (17.5%) | Total: 11 (27.5%)<br>Surgical abrasion arthroplasty/spongiolisation: 7 (17.5%)<br>Abrasion arthroplasty: 2 (5%)<br>Drilling of cartilage defect: 2 (5%) |

*continued*

***TABLE 15*** *Patient characteristics (cont'd)*

| Study | *n* | Mean age (years) | Defect size ($cm^2$) | Aetiology | Defect site | Previous surgery |
|---|---|---|---|---|---|---|
| Knutsen, 2004[63]<br>Norway<br><br>ACI vs microfracture<br><br>RCT<br><br>Follow-up: 2 years | 80 | 32.3 | 4.8 | Trauma: 65%<br>OCD: 28%<br>Other: not specified: 7% | Median femoral condyle: 89%<br>Lateral femoral condyle: 11% | Anterior cruciate ligament reconstruction (15 patients, 19%)<br>Meniscal surgery (14 patients, 18%)<br>arthroscopic lavage and débridement (29 patients, 36%)<br>Pridie drilling (3 patients, 4%)<br>Operations for OCD such as drilling or fixation of a fragment (13 patients, 16%) |
| Basad, 2004[62]<br>Germany<br><br>MACI vs microfracture<br><br>RCT<br><br>Follow-up: up to 2 years | 46 | 33 | 2–10 | Post-traumatic, no details | Femoral condyle or retropatellar, no details | Not stated |

***TABLE 16*** *Clinical outcomes*

| Study | *n* | Minimum follow-up | Clinical outcome | | | | Adverse effects and need for further surgery |
|---|---|---|---|---|---|---|---|
| Bentley, 2003[64] | 100 | 1 year | | **ACI** | **Mosaicplasty** | | **Complications** |
| | | | **Cincinnati Rating System for all defects** | | | | 3 (3%) patients were slow to mobilise and required manipulation under anaesthesia; one of these required arthroscopy and arthrolysis to mobilise knee; one patient developed calf-vein thrombosis and required anticoagulants; one patient developed a superficial infection (settled rapidly with a 5-day course of oral antibiotics) |
| | | | Number | 58 (100%) | 42 (100%) | | |
| | | | Excellent | 23 (40%) | 9 (21%) | | |
| | | | Good | 28 (48%) | 20 (48%) | | |
| | | | Fair | 7 (12%) | 6 (14%) | | |
| | | | Poor | 0 (0%) | 7 (17%) | | |
| | | | Excellent or good | 51 (88%) | 29 (69%) | $p$ = ns | |
| | | | **Cincinnati Rating System for medial femoral condyle defects** | | | | **Further surgery** |
| | | | | | | | Not reported |
| | | | Number | 24 (100%) | 29 (100%) | | |
| | | | Excellent | 11 (46%) | 6 (21%) | | |
| | | | Good | 10 (42%) | 15 (52%) | | |
| | | | Fair | 3 (12%) | 4 (14%) | | |
| | | | Poor | 0 (0%) | 4 (14%) | | |
| | | | Excellent or good | 21 (88%) | 21 (74%) | $p < 0.05$ | |
| | | | **Cincinnati Rating System for lateral femoral condyle defects** | | | | |
| | | | Number | 13 (100%) | 5(100%) | | |
| | | | Excellent | 7 (54%) | 2 (40%) | | |
| | | | Good | 5 (38%) | | | |
| | | | Fair | 1 (8%) | 2 (40%) | | |
| | | | Poor | 0 (0%) | 1 (20%) | | |
| | | | Excellent or good | 12 (92%) | 2 (40%) | $p$ = ns | |
| | | | **Cincinnati Rating System for patellar defects** | | | | |
| | | | Number | 20 (100%) | 5(100%) | | |
| | | | Excellent | 5 (25%) | | | |
| | | | Good | 12 (60%) | 3 (60%) | | |
| | | | Fair | 3 (15%) | | | |
| | | | Poor | 0 (0%) | 2 (40%) | | |
| | | | Excellent or good | 17 (85%) | 3 (60%) | $p$ = ns | |

*continued*

***TABLE 16*** *Clinical outcomes (cont'd)*

| Study | *n* | Minimum follow-up | Clinical outcome | | | | Adverse effects and need for further surgery | | |
|---|---|---|---|---|---|---|---|---|---|
| Horas, 2003[65] | 40<br>Trauma:<br>100% | 24 months | | **ACI**<br>*n* = 20 | **OCT**<br>*n* = 20 | | **Complications** | | |
| | | | | | | | | **ACI** | **OCT** |
| | | | | | | | Any | 12 | 12 |
| | | | | | | | None | 8 | 8 |
| | | | **Modified Lysholm score** | | | | | | |
| | | | Baseline | 24.9 | 28.45 | | **Further surgery** | | |
| | | | 3 months | 27.55 | 27.95 | | | **ACI** | **OCT** |
| | | | 6 months | 45.75 | 53.45 | $p$ = ns | Any | 8 | 9 |
| | | | 12 months | 57.50 | 68.25 | $p < 0.001$ | None | 12 | 11 |
| | | | 24 months | 66.75 | 72.70 | $p < 0.05$ | | | |
| | | | **Meyers score** | | | | | | |
| | | | Baseline | 7.20 | 7.85 | | | | |
| | | | 3 months | 8.50 | 7.85 | | | | |
| | | | 6 months | 12.05 | 13.75 | | | | |
| | | | 12 months | 14.15 | 15.90 | | | | |
| | | | 24 months | 15.90 | 16.75 | | | | |

*continued*

***TABLE 16*** *Clinical outcomes (cont'd)*

| Study | *n* | Minimum follow-up | Clinical outcome | | | Adverse effects and need for further surgery | | |
|---|---|---|---|---|---|---|---|---|
| Knutsen, 2003[63] | 80 | 24 months | | **ACI** *n* = 40 | **Microfracture** *n* = 40 | **Treatment failure** (Defined as patient requiring a reoperation because of symptoms due to lack of healing of the primary treated defect. The need for shaving or trimming a lesion was not defined as failure) | | |
| | | | **Lysholm score** | | | *ACI:* 2/40 (5%) at 6 and 18 months<br>*Microfracture:* 1/40 (2.5%) at 15 months<br>All were symptomatic and underwent revision with another cartilage treatment | | |
| | | | Baseline | 57 | 55 | | | |
| | | | 12 months | 68 | 77 | | | |
| | | | 24 months | 70 | 75 | | | |
| | | | (Values read from graph and hence approximate)<br>Both types of surgery significantly improved Lysholm scores from baseline ($p < 0.003$ for ACI and $p < 0.0001$ for microfracture); there was no significant difference between treatments at 1 or 2 years | | | **Further surgery** | | |
| | | | **Pain (0 to 100 VAS)** | | | Biopsy at 2 years | *ACI* | 32/40 (80%) |
| | | | Baseline | 54 | 53 | | *Microfracture* | 35/40 (88%) |
| | | | 12 months | 40 | 35 | Arthroscopic débridement | *ACI* | 10 (25%) |
| | | | 24 months | 35 | 31 | | *Microfracture* | 4 (10%) |
| | | | (Values read from graph and hence approximate)<br>both types of surgery significantly reduced pain from baseline ($p < 0.0001$ for both); less pain at 2 years: 78% with ACI versus 75% with microfracture; there was no significant difference between treatments at 1 or 2 years | | | For ACI, shaving was done mainly because of symptomatic tissue hypertrophy; for microfracture, one patient had arthrofibrosis (needed manipulation and operative release) and 3 had minor débridement | | |
| | | | **SF-36 physical component** | | | | | |
| | | | Baseline | 41 | 37 | | | |
| | | | 12 months | 42.5 | 41 | | | |
| | | | 24 months | 42 | 46 | | | |
| | | | (Values read from graph and hence approximate)<br>Microfracture significantly improved scores on SF-36 compared with ACI at 2 years ($p < 0.005$); after adjusting for pre-operative scores, microfracture still significantly improved SF-36 physical component cores compared with ACI ($p = 0.01$); there was no significant difference between treatments in the SF-26 mental health subscale | | | | | |

*continued*

**TABLE 16** *Clinical outcomes (cont'd)*

| Study | *n* | Minimum follow-up | Clinical outcome | | | Adverse effects and need for further surgery |
|---|---|---|---|---|---|---|
| Basad, 2004[62] | 46 | 12 months | Outcomes at 1 year (compared to baseline) | | | Not reported |
| | | | | **MACI** | **Microfracture** | |
| | | | | *n* = 10 | *n* = 9 | |
| | | | Meyers score | + 6.5 | + 1.9 | |
| | | | Lysholm–Gillquist score | +27.4 | + 4.1 | |
| | | | Tegner–Lysholm score | +32.6 | +15.3 | |

**TABLE 17** *Case series with long-term outcomes (at least 2 years)*

| Study | Follow-up (years) | *n* | Good or excellent outcome | Adverse effects or need for further surgery |
|---|---|---|---|---|
| **ACI** | | | | |
| Petersen *et al.*, 2000[68] | 2–9 years | 101 | 92% isolated femoral chondyle, 67% multiple lesions, 89% OCD, 65% patella, 75% femoral chondyle with anterior cruciate ligament reconstruction | 52 adverse events: 3 superficial wound infections, 1 post-operative fever, 2 post-operative haematomas, 10 intra-articular adhesions, 26 periosteal hypertrophies, 7 graft failures |
| Peterson *et al.*, 2002[70] | 5–11 | 61 | 82% at 2 years, 84% at 5–11 years | 10 treatment failures |
| Peterson *et al.*, 2003[69] | 2–10 | 58 | 91% at 5.6 years | 2 early failures |
| **Natural history** | | | | |
| Prakash and Learmonth, 2002[18] | 9 years | 15 knees, 12 patients | Healed lesion in 6/7 patients under 18 years | Signs of osteoarthritis in 6/8 patients over 18 years |
| **Microfracture** | | | | |
| Blevins *et al.*, 1998[71] | 3.7 ± 1.4 years | 38 high-level and 140 recreational athletes | Of 31 high-level athletes, 77% returned to competition, 71% reported to be equal or superior to preinjury level | Not systematically reported, no reflex sympathetic dystrophy, occasional local pain |
| Steadman *et al.*, 2003[72] | 11 years | 75 knees, 72 patients | At 7 years, 80% rated themselves as 'improved' | No peri-operative complications |
| **Mosaicplasty** | | | | |
| Hangody and Füles, 2003[73] | 3–6 years | 578 (plus a number of non-knee mosaicplasties) | 92% of femoral condylar, 88% of tibial resurfacing, 81% of patellar, trochlear or both | In entire series (*n* = 652), 4 deep infections, 34 painful haemarthroses, 2 thromboembolic complications |

# Appendix 7
# Excluded studies

The following studies were retrieved but not used.

Adirim TA, Cheng TL. Overview of injuries in the young athlete. *Sports Med* 2003;**33**:75–81. [*Not relevant.*]

Allgood P. Arthroscopic lavage for knee osteoarthritis. *STEER* 2003;**3**(3):I. [*Osteoarthritis.*]

Anderson AF, Fu FH, Mandelbaum B, Browne JE, Moseley B, Erggelet C, *et al*. A controlled study of autologous chondrocyte implantation versus microfracture for articular cartilage lesions of the femur. AAOS abstract 051 at 2003 annual meeting. [*Only abstract available, and appears to be two parallel case series not an RCT. See also abstract 023 from 2002 AAOS meeting.*]

Bahuaud J, Maitrot RC, Bouvet R, Kerdiles N, Tovagliaro F, Synave J, *et al*. Implantation de chondrocytes autologues pour lesions cartilagineuses du sujet jeune. *Chirurgie* 1998;**123**:568–71.

Bert JM. Role of abrasion arthroplasty and debridement in the management of osteoarthritis of the knee. *Osteoarthritis* 1993;**19**:725–39.

Bobic V, Morgan CD, Carter T. Osteochondral autologous graft transfer. *Operative Techniques in Sports Medicine* 2000:**8**:168–78. [*Technical review.*]

Bouwmeester PSJM, Kuijer R, Homminga GN, Bulstra SK, Geesink RGT. A retrospective analysis of two independent prospective cartilage repair studies: autogenous perichondrial grafting versus subchondral drilling 10 years post-surgery. *J Orthop Res* 2002; **20**:267–73. [*Rib cartilage transplant to knee.*]

Bugbee WD, Convery FR. Complex topics in knee surgery: osteochondral allograft transplantation. *Clin Sports Med* 1999;**18**:67. [*Cadaver allografts.*]

Chang RW, Falconer J, Stulberg SD, Arnold WJ, Manheinm LM, Dyer AR. A randomised controlled trial of arthroscopic surgery versus closed-needle joint lavage for patients with osteoarthritis of the knee. *Arthritis Rheum* 1993;**36**:289–96. [*Osteoarthritis.*]

Delcogliano A, Caporaso A, Menghi A, Rinonapoli G, Chiossi S. Results of autologous osteochondral grafts in chondral lesions of the knee. *Minerva Chir* 2002; **57**:273–81. [*Case series.*]

Gill TJ. The treatment of articular cartilage defects using microfracture and debridement. *American Journal of Knee Surgery* 2000;**13**:33–40. [*Small case series, limited information on results.*]

Gillogly S, Newfield DM. Treatment of articular cartilage defects of the knee with autologous chondrocyte implantation. *Medscape General Medicine* 2000;**2**. [*Good review, now out of date.*]

Fisher NM, Gresham GE, Abrams M, Hicks J, Horrigan D, Pendergast DR. Quantitative effects of physical therapy on muscular and functional performance on subjects with osteoarthritis of the knees. *Arch Phys Med Rehabil* 1993;**74**:840. [*Osteoarthritis.*]

Hamby TS, Gillogly SD, Peterson L. Treatment of patellofemoral articular cartilage injuries with autologous chondrocyte implantation. *Operative Techniques in Sports Medicine* 2002;**10**:129–35. [*Technical note.*]

Hangody L, Kish G, Karpati Z, Szerb I, Udvarhelyi I. Arthroscopic autogenous osteochondral mosaicplasty for the treatment of femoral condylar articular defects. *Knee Surg Sports Traumatol Arthrosc* 1997;**5**:262–7. [*Superseded by later papers.*]

Hangody L, Kish G, Karpati Z, Udvarhelyi I, Szigeti I, Bely M. Mosaicplasty for the treatment of articular cartilage defects: application in clinical practice. *Orthopedics* 1998;**21**:751–6. [*Early results; superseded.*]

Hangody L, Feczko P, Bartha L, Bodo G, Kish G. Mosaicplasty for the treatment of articular defects of the knee and ankle. *Clin Orthop* 2001;**391S**:S328–36. [*Superseded by later papers.*]

Ike RW, Arnold WJ, Rothschild EW, Shaw L, Tidal Irrigation Cooperating Group. Tidal irrigation versus conservative medical management in patients with osteoarthritis of the knee: a prospective randomised study. *J Rheumatol* 1992;**19**:772–9. [*Osteoarthritis.*]

Jerosch J, Filler T, Peuker E. Is there an option for harvesting autologous osteochondral grafts without damaging weight-bearing areas in the knee joint? *Knee Surg Sports Traumatol Arthrosc* 2000;**8**:237–40. [*Technical note.*]

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Jurvelin JK, Peterson L, Lindahl A. Kiviranta IK, Vasara A. Arthroscopic and biomechanical evaluation of

cartilage repair tissues one year after autologous chondrocyte transplantation. AAOS 2003 meeting, abstract P354. [*Abstract only; case series.*]

Litzke L-F, Wagner E, Baumgaertner W, Hetzel U, Josimovic O, Libera J. Repair of extensive articular cartilage defects in horses by autologous chondrocyte transplantation. *Ann Biomed Eng* 2004;**32**:57–69. [*Study in horses. From manufacturer.*]

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Micheli LJ, Mosely B, Anderson AF, Browne JE, Erggelet C, Arciero R, *et al*. Articular cartilage defects in young patients: treatment with autologous chondrocyte implantation. AAOS March 2004 meeting, paper 022. [*Abstract, case series.*]

Minas T, Nehrer S. Current concepts in the treatment of articular cartilage defects. *Orthopedics* 1997;**20**:525–38. [*Good but superseded review.*]

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Ogilvie-Harris DJ, Fitsialos DP. Arthroscopic management of the degenerative knee. *Arthroscopy* 1991;**7**:151–7. [*Old case series.*]

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***We look forward to hearing from you.***

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ISSN 1366-5278