NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

MULTIPLE TECHNOLOGY APPRAISAL

Autologous chondrocyte implantation for repairing symptomatic articular cartilage defects of the knee (including a review of TA89) [ID686]

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Additional information submitted following the April 2015 Committee meeting** from:
   - British Association for Surgery of the Knee – submissions from patients
   - Robert Jones and Agnes Hunt Hospital
     The Robert Jones and Agnes Hunt Hospital also submitted two unpublished papers which were sent to the Assessment Group. These papers are confidential (academic-in-confidence)
   - Vericel

3. **Additional analyses** prepared by the Assessment Group in March 2016

4. **Consultee and commentator comments on the March 2016 additional analyses** from:
   - British Association for Surgery of the Knee
   - Robert Jones and Agnes Hunt Hospital
   - Vericel

5. **Addendum to Previous Reports** prepared by the Assessment Group in May 2017

6. **Assessment Group Reponse to comments**

7. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Robert Jones & Agnes Hunt Orthopaedic & District Hospital NHS Trust (RJAH)
   - Sobi
   - Vericel
   - British Association for Surgery of the Knee
   - British Orthopaedic Association
   - Cell Therapy Catapult
   - Healthcare Improvement Scotland
   - Warwick Evidence

8. **Comments on the Appraisal Consultation Document from experts:**
   - Leela Biant - clinical Expert, nominated by the British Association for

Surgery of the Knee
- Mr John Keating – clinical Expert, nominated by Healthcare Improvement Scotland

9. Comments on the Appraisal Consultation Document received through the NICE website

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal

Autologous chondrocyte implantation for treating symptomatic articular cartilage defects of the knee

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD) issued in March 2015

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation.

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment [sic]	Response
Robert Jones and Agnes Hunt Orthopaedic and District Hospital NHS Trust	We thank NICE for providing us with the opportunity to comment on its draft document and preliminary recommendations. Our overall position is that we believe that ACI should be an option for NHS patients, in the context of ongoing study and development. By and large, we therefore agree with the preliminary recommendation that ACI should be undertaken within the context of further research. We realise in particular that any cost-savings from ACI over alternatives such as microfracture would come from long-term savings on subsequent treatments such as knee replacement. Solid long-term data on which to base such a decision is scarce, making a decision difficult. We would like to make three specific comments. The first relates to the funding implications of the proposed recommendation, and the others addresses some specific aspects of our submitted data and its use in making the decision.	Comments noted. The recommendations have been updated following consideration of additional analyses from the assessment group, which were requested from the Appraisal Committee at its second meeting in April 2015 (when it discussed these consultation comments).
Robert Jones and Agnes Hunt Orthopaedic and District Hospital NHS Trust	**Comment 1** We welcome the replacement of the phrase "**not recommended** for the treatment of articular cartilage defects of the knee joint except in the context of ongoing or new clinical studies", used in the old appraisal TA89, with the proposed phrase "**recommended** only in research for repairing symptomatic articular cartilage defects of the knee". In our experience some health bodies would not read the old guidance beyond "not recommended". The proposed more positive wording seems a step forward. Nevertheless, we think the recommendation needs some further modification relating to 'only	Comments noted on issues surrounding 'only in research' recommendation in the Appraisal Consultation Document. The recommendations have been updated following consideration of additional analyses from the assessment group, which were requested from the Appraisal Committee at its second meeting in

Consultee	Comment [sic]	Response
	in research' because of funding implications for existing and new clinical studies. In line with the two earlier NICE recommendations on ACI (TA16 and TA89), we have always entered our ACI patients in an ethically approved cohort study to find out their long-term results (adopted as UKCRN no. 9570). At the moment, we are still adding to that cohort study. Two years ago, we started a new randomized clinical trial of autologous cell therapies to treat knee cartilage defects, including ACI (ASCOT; UKCRN no. 12383). These studies receive funding from Arthritis Research UK, the MRC and the Orthopaedic Institute in Oswestry, a local charity funding orthopaedic research. The funds pay for the infrastructure to run these trials, such as trial management, data collection, statistical analysis etcetera, and for extra clinical investigations that are needed as part of the studies. Such funding is particularly important for long-term studies, which are the only types of study able to generate the data that NICE needs. The results from the cohort study have resulted in a steady stream of publications since we started the study in 1997 (Appendix I), which have informed understanding of and treatment with ACI. This study now starts to shine a light on the long-term results of ACI (the REACT study quoted in the appraisal consultation document). Funding for the treatment costs in these UKCRN portfolio studies has so far come through the NHS. We are concerned that the new recommendation may halt funding for the ACI treatment costs within the context of research. This would deprive patients of a potentially effective treatment and would hinder NICE in their attempts to determine the long-term effectiveness of ACI. At some point in the future the answer may of course be found from a study performed outside England or Wales, but delegating research abroad in an attempt to save costs does not seem prudent. Our concerns are not without ground. In our current Randomised Controlled Trial we have treated 25 patients with ACI to date. A further 3 patients (12%) could not be treated during this time period because the funding was not approved, with the	April 2015 (when it discussed these consultation comments).

Consultee	Comment [sic]	Response
	response from NHS England being “NHS England does not have a formal commissioning policy in relation to this treatment. Autologous chondrocyte implantation is not routinely commissioned or funded”. The NICE assessment report shows that cell costs are a key driver of cost effectiveness. We manufacture cells within the NHS, keeping these treatment costs relatively modest. Indeed, during the first appraisal committee meeting on 10 February 2015 there was some incredulity around the table with respect to our costs, a point we will address later. One should however not forget that the ACI treatment was originally developed within an NHS-like environment in Sweden (the Gothenburg Medical Centre, Kungsbacka Hospital and Sahlgrenska University Hospital in Gothenburg). To this day, the Sahlgrenska University Hospital still manufactures the cells used for treatment in Gothenburg, for the very reasons of keeping down costs and allowing clinical research. Besides Oswestry, hospitals in Norway (Tromso) and Spain (Madrid) took the same approach. At the right costs, ACI can be cost effective, and perhaps the only way to achieve that in England and Wales is within the NHS. This is of course not without precedent, other examples of long-term successful supply of live human products from within the NHS are NHS Blood and Transplant, the Bone Marrow Transplant units around the country or the Haematopoietic Stem Cell Transplant service at University College London. For this reason, we ask the appraisal committee to consider the following two options. The first option is for the committee to use the recommendation “research with funding” instead of “only in research”. We know that this recommendation has never been used by NICE, but could be given if the expected ICER is well below the current threshold of £20k/QALY. The assessment report gives a strong indication that ACI can have an ICER of around £5k-7k per gained QALY, provided the cell production costs are £8,000 (reduced by 50%; Table 18-19 in the assessment report and Table III in Appendix II). Reducing them by 75% to £4,000 would achieve an ICER	

Consultee	Comment [sic]	Response
	£2k-3k/QALY (Table 18-19 in the assessment report and Table III in Appendix II below). This ICER is achieved over a lifetime horizon and therefore uses many assumptions currently not supported by solid data. However, even at a shorter time horizon of 20 years ACI is likely to be cost-effective at lower cell production costs (£8.5k/QALY assuming 50% cell costs, see details in Appendix II) and even at a 10 year horizon it would be cost-effective (£13k/QALY, see details in Appendix II). At a cell cost reduction of 75%, the 10-year horizon ICER would be £5.5k/QALY (see details in Appendix II). Interestingly the latter number, based purely on the assessment group's data, is close to the ICER of £6k/QALY that was provided in our submission. That number was based on an 8-year horizon, the current follow-up in the randomised controlled trial ACTIVE, and our current treatment costs, which rely on our (lower) cell production costs. The committee could therefore consider using the recommendation "Recommended with research" adding the qualifier that cell costs in the studies should be at most 25%-50% of the cost of £16,000 assumed in the assessment report, i.e. £4,000 to £8,000. This would encourage the NHS to fund treatment costs for the studies needed to generate robust data on ACI. Moreover, our experience shows that these prices are not unrealistic within the context of an NHS manufacturing facility. A second option for the committee would be to add a section on "Implications for the NHS", similar to the previous assessment TA89. In that section, the previous guidance read "The net budget impact on NHS expenditure in England and Wales will depend on the number of patients in, and funding arrangements for, the clinical studies recommended in Section 1.1. The Institute expects there to be some NHS expenditure on this technology." The presence of this section in TA89 has not prevented the above mentioned difficulties in obtaining treatment funding for patients in our current UKCRN portfolio trial, indicating that it may not be sufficient. For this reason, our preferred option is for the assessment committee to use the recommendation "research with funding".	

Consultee	Comment [sic]	Response
Robert Jones and Agnes Hunt Orthopaedic and District Hospital NHS Trust	**Comment 2** We were pleased that our cell production data could contribute to NICEs assessment of ACI. However, we respectfully disagree with the committee's conclusion on the true costs of the cells in section 5.16 (Cost of the cells, bottom of page 41). The current paragraph states "The Committee noted that the OsCell submission had estimated a production cost of the cells of £4125. The Committee heard from a representative of OsCell that the cost of cells included the cost of materials and staff time, but not the costs of overheads. The Committee therefore considered that OsCell had underestimated its cell costs, and that the true cost may approach that of MACI and ChondroCelect." Our estimated cell costs of £4125 per patient did not come with a breakdown because we concentrated our submission on the total costs of the ACI procedure and its comparators as they are currently reimbursed to our hospital. We would like to use this opportunity to rectify this omission and demonstrate that, contrary to the committee's conclusion, our "true" costs do not approach the costs of MACI and ChondroCelect. Our submitted costs were based on the annual hospital budget to run the facility, and built up as follows. The annual budget to run the facility is £150,000. This budget includes all direct running costs, hence the personnel, infrastructure, culturing etcetera. Additional costs are the annual costs for our Qualified Person (£12,000) and MHRA license fees (£3,000), bringing the total annual costs to £165,000. In a typical year, we treat 40 patients, which gave the estimated cell costs per patient of £4125. As the committee noted, these costs did not include general overheads and depreciation costs. Our hospital finance manager estimates the overheads as £37,000 per year. Our production facilities cost around £100,000 and depreciate over 10 years, adding an extra £10,000 per year. We therefore estimate these extra costs as £47,000 per year, or £1,175 per	Comment noted. In its third meeting (May 2017) the committee noted the most recent cell cost estimate from OsCell. This was presented in OsCell's response to the assessment group's additional analyses (carried out after the second committee meeting in April 2015).

Consultee	Comment [sic]	Response
	patient. This would bring our "true" cell production costs to £5,300 per patient. As the committee will note, this cost does not approach that of MACI and ChondroCelect but amounts to 33% of the cell costs of £16,000 assumed in the committee's assessment. To assure ourselves that our costs do not underestimate the "true" costs we asked our colleagues at hospitals in Gothenburg and Madrid, who obtain cells through similar in-house facilities, for their costs. The facility at the Sahlgrenska University Hospital in Gothenburg charges €5,500-€6,000 (£4,000-£4,400) per patient, which covers their costs. The facility in Madrid charges €2,000 (£1,500) per patient, covering their costs. In light of these figures from other facilities, we think our all-in estimate of £5,300 is unlikely to be under-priced.	
Robert Jones and Agnes Hunt Orthopaedic and District Hospital NHS Trust	**Comment 3** The committee considered a possible bias in the randomised controlled trial ACTIVE with respect to rehabilitation regimes. Specifically, "the Committee considered it possible that, because of the open-label design, people having [been randomised to] ACI having been advised of the longer rehabilitation time compared to microfracture may have better adhered to rehabilitation in the hope of promised long-term benefits". We would like to comment that the results from the trial show no evidence at all of a slower rehabilitation by patients who were randomised to the ACI arm. We think this is shown most clearly by the evolution over time of the Cincinnati Sports Activity Score, which we provided in our submission (page 25, Fig 4) and reproduce below. Rehabilitation would most strongly affect the sports activity of patients. Clearly, patients in both the ACI and control group held back from sports activity at the 3 months point to allow for their rehabilitation. At 6 months however, both groups had increased their sports activity to a level that would be largely sustained over the 4.5 ensuing years. Stronger even, the graph suggests that patients randomized to ACI had a 5 points lower baseline sports activity score, but after 6 months the sports activity scores were	Comment noted. The statement "the Committee considered it possible that, because of the open-label design, people having [been randomised to] ACI having been advised of the longer rehabilitation time compared to microfracture may have better adhered to rehabilitation in the hope of promised long-term benefits" does not appear in the Final Appraisal Determination.

Consultee	Comment [sic]	Response
	nearly identical in the two groups. We believe this data clearly shows that the committee's consideration that the patients randomised to ACI "may have better adhered to rehabilitation in the hope of promised long-term benefits" is not reflected in their reported activity levels. On the contrary, we think the data more likely shows that patients randomised to ACI decided to cash in early on such a promise. *Figure 1 Evolution over time of Cincinnati Sports Activity Scale scores for patients in the ACTIVE trial randomised to ACI or "Standard" (i.e. control). 95% CIs are shown for each treatment (not reproduced here please see the company's response to ACD in the evaluation report)* *Appendices not reproduced here. Please see the company's response to ACD in the evaluation report*	
Sobi	The recommendation for use only in research given in the appraisal consultation document (ACD) is an understandable decision in the context of OsCell (for which there is no published outcome or safety data), given the product is unlicensed. However this may not be the most appropriate decision for ChondroCelect and MACI. Given no new data will be available in the near future, Sobi are disappointed by the Committee's provisional decision and feel that, with no ongoing trials, it effectively represents a negative recommendation for ChondroCelect. On further reflection of the available evidence, three important issues were not raised in the ACD. • Firstly, while the ACTIVE trial (based in the OsCell centre) is due to provide ten year data, it is a non-randomised study with a 'pragmatic comparator' arm. The quality of its data is uncertain, and patient numbers in the long term are likely to be low (with potentially	Comments noted. The recommendations have been updated following consideration of additional analyses from the assessment group, which were requested from the Appraisal Committee at its second meeting in April 2015 (when it discussed these consultation comments). The status of the marketing authorisation for MACI (suspended) and ChondroCelect (withdrawn) have been stated in the Final Appraisal Determination. Thank you for the additional analyses provided to NICE and the Appraisal Committee in

Consultee	Comment [sic]	Response
	informative dropout). While efficacy results were not presented, the utility data presented were not of a high standard. • Secondly, although MACI has a well conducted randomised controlled trial with several years follow up, the marketing authorisation for this product is currently suspended (and has been since December, 2014). • Finally, the marketing authorisation for ChondroCelect is misrepresented in section 5.6 of the ACD. Although the trial for ChondroCelect is in patients with a lesion size of up to 5cm^2, the license allows treatment of all patients – in the Belgian registry data, 40% of patients had lesions over 5cm^2. For ChondroCelect, the pivotal randomised trial, TIG/ACT/01/2000, provides data to five years. This is much more than the majority of interventions assessed by NICE and, as stated by the assessment group, is a high quality study. The final five year reporting from this study has also completed (the initial study was powered for twelve month outcomes). With no ongoing trials for ChondroCelect, use in research would require the establishment of a registry. Sobi understand that the Committee was faced with uncertainty regarding the most appropriate economic modelling of the disease area (though the Sobi manufacturer's model was closest to the clinical practice), as well as uncertainty on long term treatment effectiveness. To this end, we have provided additional data and analyses where issues have been raised in the ACD, issues identified by the committee, and sensitivity analyses around uncertainties. We hope that these may provide the basis for a positive recommendation to be made. Our revised modelling (with all changes suggested by the committee), and including more appropriate modelling of effectiveness (parametric curve fitting), provides an incremental cost-effectiveness ratio (ICER) of £25,961	response to the appraisal consultation document. These were presented to committee at the second committee meeting. The marketing authorisation for ChondroCelect was withdrawn (for commercial reasons) by the marketing authorisation holder between the second and third committee meetings. The committee used the assessment group's model in its decision making because this incorporated additional analyses requested by NICE at the second meeting. The Final Appraisal Determination (section 3.14) noted that the ChondroCelect model had been presented over the course of the appraisal and that it had a similar structure to the assessment group's model.

Consultee	Comment [sic]	Response
	compared to microfracture. The ICER is £14,727 using a discount rate of 1.5% to account for the long term benefits of ACI. Likewise excluding treatment failures due to the old technique used in the trial, the ICER falls to £18,500. The major changes generating this new ICER are: • New analysis of SF-36 data collected in the TIG/ACT trial (now mapped to EQ-5D) • Revised utility values for patients who did not receive a re-intervention (identified by the committee) • Including a minimum age restriction for knee replacement, and the possibility of a partial replacement • Changes to unit costs • An exploratory comparison with MACI • Extrapolation of treatment failure using parametric curves (not a line of best fit) We hope that our additional analyses and modelling are sufficient for the Committee to issue a positive final recommendation. However if a use in research recommendation is viewed by the Committee as being the most appropriate, Sobi request that a third Appraisal Committee meeting be held with a gap of at least 8 weeks from the publication of any decision. This will allow Sobi the chance to organise the creation of a registry, which can then be used to collect longer term data, if viewed as sufficient by the NICE Committee. This will ensure that both use and research do happen, and without which, the decision would effectively be a 'no'. *Additional data and analyses provided by the company in response to the ACD are not reproduced here. Please see company's response to ACD in the evaluation report.*	
Vericel	**Appraisal Committee:**	Comments noted. The recommendations have been updated following consideration of

Consultee	Comment [sic]	Response
	"Autologous chondrocyte implantation is recommended only in research for repairing symptomatic articular cartilage defects of the knee. Research should include clinical trials and observational studies designed to measure the long-term benefits of autologous chondrocyte implantation" **Vericel Response:** Given the level of evidence (clinical trials and observational cohort studies), and the extent of the long-term evidence available both from randomised and observational studies, a positive recommendation for MACI/ACI treatment as first -line therapy should be allowed by the NHS. *Level of Evidence* Autologous Chondrocyte implantation (ACI) was first introduced in 1987 by Professors Lars Peterson, Mats Brittberg, Anders Lindahl from Gothenburg Sweden. Since then thousands of patients have been treated with ACI around the world. ACI has a long-standing, well-established history of consistent outcomes and high patient satisfaction. In the last ten years, ACI technology has further been evaluated in a number of randomised studies. Eleven of those studies have evaluated ACI versus another repair technique. Seven of the eleven studies showed that ACI to be superior over the other technique. 1 2 3 4 5 6 7 8 9 10 11 Two of the randomised clinical trials, the SUMMIT trial for MACI and ChondroCelect®, are registered as Advanced Therapy Medicinal Products (ATMP) under EMA regulations, and have thus passed all requirements for evidenced-based standards for clinical outcomes. To meet EMA regulations and standards for phase 3 clinical trials, the number of patients included in the studies are determined based on the power to detect a difference in treatment between randomised treatment arms. For the SUMMIT study, given the length of follow-up and taking into account a possible 15% reduction in sample size due to early discontinuation of patients from the study, this calculation resulted in a total sample size of 144 patients (72 in each treatment arm).	additional analyses from the assessment group, which were requested from the Appraisal Committee at its second meeting in April 2015 (when it discussed these consultation comments). A research recommendation is no longer included in the Final Appraisal Determination.

Consultee	Comment [sic]	Response
	The level of evidence, utilization and majority opinion amongst cartilage experts from the British Orthopaedic Society, the British Association for Surgery of the Knee (BASK) and board members of the International Cartilage Repair Society confirms the wide acceptance of ACI for the treatment of articular cartilage defects. In a consensus statement on surgical technique that was published following a consensus meeting of leading European orthopaedic surgeons specializing in cartilage repair, Steinwachs *et al* stated “Autologous chondrocyte transplantation has become an established therapy for full-thickness cartilage defects.”12 A similar article, the UK cartilage consensus paper, with more than 100 participating surgeons, is to be published in Journal of Bone and Joint Surgery (JBJS) in April, 2015. This was part of the initial assessment review. *Long-term Evidence of Effect* Multiple generations of ACI have been used for treatment of cartilage repair, ranging from cultured chondrocytes injected as a suspension under a periosteal membrane to cells seeded on or in matrices 4 for safer delivery. The active ingredient is the same across generations, namely the cultured chondrocytes that are programmed to produce cartilage, rendering all forms relevant when comparing outcomes. Nine studies of ACI have been published with greater than ten years of follow-up, and some studies have as long as 20 years of follow-up. These studies have shown that ACI produces a robust, durable repair tissue that allows patients to return to active and productive lives (See Table 3 for additional detailed information). There are another nine publications with 5 to 9 years of follow-up. The majority of these have been academic cohort studies and support the findings that ACI is a durable repair (Table 1). While the types of studies vary, including academic randomised and cohort studies, the pattern of data show repeatability in the durability of efficacy across studies. Given the level and extent of the shorter-term (2-year) and longer-term (up to 20 years) evidence available both from randomized clinical trials and observational studies, and the fact that ACI was found to be cost-effective under most assumptions (see additional details in Section 7), a positive	Comment noted. At the request of the Appraisal Committee, the assessment produced additional analyses after the second committee meeting using all suitable data on ACI (all generations and including observational data).

Consultee	Comment [sic]	Response
	recommendation for MACI/ACI technology should be allowed for use on the NHS. **Our recommendation to the committee is** *to allow the use of ACI, following accepted treatment algorithms and EMA guidelines, to allow the physician to decide the best course of treatment, especially for those cases involving higher complexity where there are a few treatment options*	Comment noted. In making its recommendations the committee determined the groups in whom ACI was likely to be cost-effective.
Vericel	**2 Clinical Comparators and Evidence of Effect** **2.1 Microfracture as a comparator** **Appraisal Committee:** **"Microfracture involves drilling small holes through the bone under the damaged cartilage to allow bone marrow cells to fill the damaged area and to differentiate into chondrocytes."** **Vericel Response:** Microfracture is not considered a drilling procedure, but is a perforation of the subchondral bone plate to reach intracortical vessels. The resulting bleeding from penetrating the subchondral plate develops into a blood clot that functions as a scaffold to attract cells from the bone marrow. Such cells could be mesenchymal stem cells (MSC) that may go into a chondrogeneic lineage producing a fibrocartilaginous tissue repair. However, they are not pure chondrocytes and there is no evidence to show the actual number of stem cells involved in this repair process. 13	Comments noted. This statement is not included in the Final Appraisal Determination (The template for Appraisal Consultation Documents and Final Appraisal Determinations has changed since the Appraisal Consultation Document for this appraisal was published, and no longer includes a background section)
Vericel	**Appraisal Committee:** **"Microfracture is normally used for lesion sizes of less than 13 cm2".** **Vericel Response:** *Lesion Size Appropriate for Microfracture Treatment* The current literature references on microfracture is consistent with microfracture used only for smaller lesions. Specifically, using microfracture in larger lesions damages the subchondral bone, which causes a change the architecture of the cartilage bone junction causing it to become much stiffer	Comment noted. This statement is not in the Final Appraisal Determination. Section 3.1 now states "The committee was aware of a published Consensus Paper, which describes the consensus of 104 UK surgeons with specialist knowledge of surgical repair techniques for articular chondrocyte defects of the knee, and which states that microfracture is

Consultee	Comment [sic]	Response
	and increasing stress and shear forces at the cartilage-bone interface with larger lesions. 14 15 16 *17* Therefore, in patients with cartilage lesions >4cm2 there are few treatment options, and this is where ACI has been found to be effective (see also Lesion size ACI vs Microfracture, below). The Mithoefer systematic review18, describes the lesion size in which microfracture performs the best, namely in smaller lesions (< 2-3cm2) that are well contained, shouldered edges, not beveled to help protect against the opposing forces. Younger patients (<45 years of age), with a BMI <30 and a duration of symptoms of <12 months are also key predictors. In addition it is important to note that the result of the procedure is highly dependent on the compliance with rehabilitation protocol. Mithoefer's review suggests that microfracture is not preferred for larger defects due to it creates fibrocartilage repair tissue, the wear characteristics of the repair tissue are unknown over time and the fill rate can be unpredictable. A small well-shouldered chondral defect prevents damage to the opposing surface, because the shoulders of the defect supports the subchondral bone. This is where a fibrocartilage repair tissue works with lesions between 2 to 3 cm2. For larger lesions, there is an overload on the cartilage rims and there are forces working against the opposing subchondral bone. In this situation, a more durable repair tissue is needed with mechanical properties closer to hyaline tissue. Peterson et al, 2002, examined the biomechanical properties with long-term follow-up.19 Another comparator that was mentioned in the assessment report, is mosaicplasty. This procedure is mostly used for small areas of damage (less than 2 cm2) and indicated mainly for osteochondral lesions and defects where 1-2 plugs can sufficiently fill the symptomatic defect. *Lesion Size ACI vs Microfracture* It is clear that ACI is suitable for a wider range of lesions sizes than microfracture. This was reported in a publication of the results of SUMMIT20, where a range of 3 to 20 cm2 was included, and also in the	less effective in articular cartilage defects over 2 cm^2 and, and that ACI is the surgery of choice for articular cartilage defects larger than 2 cm^2.

Consultee	Comment [sic]	Response
	European Public Assessment Report (EPAR) of MACI where the EMA concluded: “the potential effect of lesion size was considered important by the Committees. In a subgroup analysis of the group with larger lesions (> 4 cm2) in the pivotal study, MACI was superior to MFX (KOOS response rates 97% vs. 77%), while a positive trend was seen for the individual components of the co-primary efficacy parameter for both pain and function. However, in the group with smaller lesions (< 4 cm²), where microfracture is considered the treatment of choice of choice, there was also a benefit for MACI (KOOS response rates (78% vs. 61%). Overall, the 6 Committees concluded that the benefit of MACI is not restricted to a particular size of lesion and can be used for lesions from 3 to 20 cm2.” 21 This is further confirmed by the systematic reviews by Oussedik26 that also concludes that in lesions greater than 4 cm2, ACI has been shown to be more effective than microfracture.	
Vericel	**2.2 Clinical Effectiveness Evidence** **2.2.1 SUMMIT Trial** **2.2.1.1 Trial Size** To meet EMA regulations and standards for phase 3 clinical trials, the number of patients included in the studies are determined based on the power to detect a difference in treatment between randomised treatment arms. For the SUMMIT study, given the length of follow-up and taking into account a possible 15% reduction of patients due to early discontinuation from the study, this calculation resulted in a total sample size of 144 patients (72 in each treatment arm).	Comment noted.
Vericel	**2.2.1.2 Primary Endpoint (co-primary KOOS pain and function)** The SUMMIT trial was based on superiority on the Knee injury and Osteoarthritis Outcome Score (KOOS). The Appraisal Committee concluded that the KOOS is the most appropriate score to assess clinical effectiveness. KOOS is a validated patient outcome tool designed to assess the patient’s opinion of his/her knee and associated problems. The sensitivity of the	Comment noted. The discussion of the symptom scoring systems used in the trials has been deleted from the Final Appraisal Determination. This is because it was no

Consultee	Comment [sic]	Response
	KOOS scores has been validated and reliably reports changes in the five subscales of overall knee health. A 10-point improvement on KOOS represents a clinically important difference in effect of treatment. While KOOS is the preferred outcome measure, the Lysholm, Tegner and Cincinnati scores are also considered reasonable and reliable measures of pain and function and most importantly allow for intra-study comparisons from a historical perspective.	longer considered a key consideration in the committee's decision making.
Vericel	**2.2.1.3 Study Design and Results** The SUMMIT trial is the only cartilage trial designed to demonstrate Superiority of Matrix-induced autologous chondrocyte implant versus Microfracture in patients with symptomatic articular cartilage defects in the knee. SUMMIT represents the largest, most rigorous GCP, randomized, controlled trial of cartilage repair to date. It was designed to meet the new ATMP regulations for EMA. To date, the SUMMIT trial is viewed as one of the most comprehensive trial in cartilage repair field based upon its unique design, as is evident from a statement by the Committee for Medicinal Products for Human Use (CHMP). They noted that the approval of MACI was based on "the robust clinical data from a prospective study showing clinically relevant effects and confirming an acceptable and manageable safety profile, the Committees concluded that the benefit/risk balance of MACI for the repair of symptomatic, full-thickness cartilage defects of the knee is positive. The clinical study data was further supported by information from published literature as MACI has been available in some European countries since 1998 in accordance with national legislation before coming under the 7 new legal framework for advanced therapies. MACI has completed all the requirements for licensing as the first advanced-therapy medicine to be combined with a medical device." 21 Factors that led to this conclusion include: • Sites were trained in standardized microfracture and MACI implant surgical and rehab procedures to minimize investigator variability	Comments noted. The data from SUMMIT was considered by the appraisal committee in its decision making (Final Appraisal Determination sections 3.5 and 3.6).

Consultee	Comment [sic]	Response
	• Validated clinical outcomes; Histology (ICRS II) scores used. • MRI to assess defect fill • Response rate based on KOOS pain and function ● Comprehensive patient follow-up ● High number of patients completing the study (intent-to-treat population) • 70/72 MACI patients, and 67/72 microfracture patients completed the trial ● 5-year extension study in progress for further follow up SUMMIT screened 189 patients, and 144 patients were randomised (72 patients in each study arm). At Week 104 (Year 2), the improvement in the MACI group compared with microfracture with regards to the co-primary endpoint of KOOS pain and function (SRA) was clinically and statistically significant (p = 0.001. The partial correlation (p-value) for the primary analysis was 0.746 (p <0.001) indicating a high strength of dependence of the co-primary endpoints. Secondary endpoints also demonstrated statistically significant differences favoring MACI compared to microfracture at Week 104; these included activities of daily living (p <0.001), knee-related quality of life (p = 0.029), other symptoms (p <0.001), and modified Cincinnati knee rating system overall score (p = 0.002). The primary efficacy endpoint was corroborated by other validated patient-reported outcome measures included in the study (SF-12 physical health score, and IKDC Subjective Knee Evaluation). In addition, significantly more patients treated with MACI (87.5%) met the responder analysis criteria (defined as improvement from Baseline to Week 104 of at least 10 points in both KOOS Pain and Function [SRA]) than patients treated with microfracture (68.06%) (p = 0.016). The planned analyses for treatment failure rates and treatment group differences were not possible due to the small number of per protocol	

Consultee	Comment [sic]	Response
	treatment failure cases. Only 5 patients (1 MACI and 4 microfracture) were confirmed as treatment failures by the Independent Treatment Failure Evaluation Committee.	
Vericel	**2.2.2 Additional ACI Evidence (Carticel®)** In the US, the FDA required two post-approval studies for Carticel®, autologous chondrocytes delivered as a suspension and secured by periosteal flap. As a consequence of the post-approval requirement, the Registry-based study and a phase IV study, the STAR study, were conducted. These studies were designed to collect multicenter assessment of outcomes in the general orthopaedic practice. The strengths of the Registry-based and STAR study were that both involved prospective data collection, had an independent oversight board, used *a priori* cohort identification and analysis plans, involved a HIPAA 8 compliant database, and met AHRQ guidelines for high quality registry design. Based upon the successful outcome of these studies, ACI was approved by the FDA in 2006 and 85% of the insurance companies have medical policy to cover ACI for full-thickness symptomatic cartilage defects. The MACI STAR, and Registry-based studies used the same active ingredient, autologous chondrocytes, manufactured in the same facility. Although the designs of the 3 ACI studies (SUMMIT, STAR, and Registry-based) were different (ie, randomized clinical trial, open-label cohort, and registry-based observational, respectively), efficacy results of within-patient change from baseline status following autologous cell treatment showed a similar pattern on KOOS (SUMMIT and STAR; not collected in Registry-based) and modified Cincinnati scores supporting the efficacy of the autologous cells to repair the cartilage defect. Descriptions of the Carticel® studies are provided, below.	Comment noted. The recommendations from NICE technology appraisals only apply to technologies with a marketing authorisation for use in England.
Vericel	**2.2.2.1 Registry-based study** The Registry-based study was an open-label, prospective, multicenter study within-patient evaluation of patients with articular cartilage defects of the knee who had an inadequate response to a prior non-ACI intervention.22	Description noted.

Consultee	Comment [sic]	Response
	Ninety-seven patients with an average lesion size of 4.9cm2 were followed for a period of up to five years. A total of 70% of patients demonstrated both a statistically and clinically significant 4.1 point improvement with the Modified Cincinnati Rating Scale.23 A 2-point change on this scale represents a clinically meaningful difference, and thus this was largely surpassed in the Registry study.	
Vericel	**2.2.2.2 STAR study** The STAR study was a phase IV, open-label, prospective, multicenter (29 centres in total), within-patient evaluation study of patients with articular cartilage defects of the knee who had an inadequate response to a non-ACI prior surgical treatment and then subsequently received ACI. 24 The objective of the STAR study was to confirm durability and effectiveness of ACI for the labeled FDA indication.* (* US FDA-approved indication for Carticel® (autologous cultured chondrocytes) is an autologous cellular product indicated for the repair of symptomatic cartilage defects of the femoral condyle (medial, lateral or trochlea), caused by acute or repetitive trauma, in patients who have had an inadequate response to a prior arthroscopic or other surgical repair procedure (e.g., debridement, microfracture, drilling/abrasion arthroplasty, or osteochondral allograft/autograft). Carticel should only be used in conjunction with debridement, placement of a periosteal flap and rehabilitation. The independent contributions of the autologous cultured chondrocytes and other components of the therapy to outcome are unknown. Carticel is not indicated for the treatment of cartilage damage associated with generalized osteoarthritis. Carticel is not recommended for patients with total meniscectomy unless surgically reconstructed prior to or concurrent with Carticel implantation.) This study included a challenging patient population with large lesions, severe symptoms at baseline and having failed prior treatment(s). The sample size was 154 patients and the study had a length of follow-up of four years, establishing the STAR study as the largest cartilage repair study in the United States.	Description noted.

Consultee	Comment [sic]	Response
	All primary and secondary endpoints were met. ACI demonstrated sustained improvements in knee function as early as 6 months and out to 4 years (as measured by KOOS). A total of 77% of evaluable patients reported a follow-up score of “good” to “excellent.” Of all evaluable patients, 50% “very good” or “excellent” results, indicating few or no limitations participating in sports. The safety results of STAR were consistent with the known ACI safety profile. Patients in STAR presented with many clinical challenges and, as expected, subsequent surgical procedures (SSPs) were reported. A total of 49% (N=76) of patients underwent an SSP irrespective of relationship to ACI. Of the patients who underwent an SSP, 83% (63/76) underwent an arthroscopy or manipulation under anesthesia only. Lysis of adhesions was the most frequent surgical intervention performed in the first 6 months. Cartilage debridement was the most frequently performed intervention after 6 months. The most common serious adverse events (≥5% of patients), derived from STAR , include arthrofibrosis/joint adhesions, graft overgrowth, chondromalacia or chondrosis, cartilage injury, graft complication, meniscal lesion, graft delamination, and osteoarthritis. Subsequent surgical procedures were not indicative of treatment failure in STAR. Of the patients who required an SSP, 61% (46/76) did not meet the study definition of treatment failure (e.g., graft delamination or surgical procedure violating the subchondral bone).	
Vericel	**2.2.2.3 Systematic Reviews and Meta-Analyses** There are several sources of information involving either MACI or ACI. A meta-analysis by Negrin, which set out to test whether ACI was superior to microfracture, concluded that when taking into consideration only second and third generation ACIs, differences with microfracture were significant though converging over time. This was based on a review of six studies involving a total of 399 patients aged between 16 and 60 years with lesion sizes between 1 and 10 cm2.25 A systematic literature review by Ossendik indicated that ACI is more effective than microfracture, especially in lesions larger than 4 cm2. 26	Comments noted. Following the second committee meeting the assessment group carried out an updated systematic review and analyses.

Consultee	Comment [sic]	Response
	An indirect comparison of MACI versus ACI and MACI versus mosaicplasty was undertaken for an MSAC submission for MACI in Australia in January 2013. Overall, the analyses showed no significant difference between ACI and MACI in the likelihood of achieving a response to treatment. 27	
Vericel	**2.2.2.4 Long-term Follow-up Data** There is a substantial amount of data (approximately 1,000 patients reported in the publications) on longer term efficacy as shown in Table 1. These data show that at 5 years 10% of patients reported a failure with MACI. These 5-year failure rates are lower than those reported in the Appraisal Committee's Report, which used failure rates of 13.1% at three years. A consistent finding with both randomized controlled trials and the 5-year studies from Ebert28 and Marlovits29 was an early response that was maintained over time. *Table 1 Overview of long-term MACI data is not reproduced here. Please see company's response to ACD in the evaluation report* There are an additional nine studies reporting long-term data for earlier generations of ACI. The Appraisal Committee report indicated that they felt these earlier generations of ACI were of less value for this MTA. However, comparability data have shown that the active compound (cultured chondrocytes) in MACI is essentially the same as the first generation products. MACI was developed as a means of delivering the cells in a more efficient and safer method when compared to the first generation. Therefore, these long-term data from the first generations should not be considered obsolete, but rather as establishing a pattern of the long-term durability. ACI has a well-established history. From studies using the first generation techniques, long-term follow-up has been published in over ten publications. These studies provide long-term efficacy in 11 864 patients with more than ten years of follow-up, and 411 patients with between five and 10 years of follow-up.	Comments noted. Following the second committee meeting the assessment group carried out an updated systematic review and analyses. The systematic review included cohort studies and trials of all generations of ACI. The committee concluded that the assessment group had identified the best available studies to estimate the long term failure rates of ACI and microfracture (Final Appraisal Determination section 3.8).

Consultee	Comment [sic]	Response
	Table 2 below shows these nine studies of earlier ACI versions, each reporting similar failure rates, approximately 25%. This is similar to 10-year results reported with the newer versions of ACI. However at shorter time frames, ie, five years, failure rates are for third generation MACI are much lower, namely 10%. A consistent finding with the long-term results was a high patient satisfaction rate, even at 20 years of follow-up. *Table 2. Overview of long-term data earlier generation ACI data is not reproduced here. Please see company's response to ACD in the evaluation report* A systematic review by Harris of failures and complications after ACI, reported that failure rates were higher with first generation ACI-P than with second-generation ACI-C and thus confirms the observations in the studies mentioned above.41 With regards to the Assessment Group's review of additional long-term studies, the information on the Minas paper was interpreted incorrectly: This paper was cited by the Committee as not supporting ACI over microfracture for the treatment of larger lesions. The focus of the paper was examining the damage MFX causes on the subchondral bone and in case of advanced bony pathology, ACI outcomes can be affected. If the chondral lesions without significant degenerative changes to the underlying bone are considered, the Minas paper supports the long-term efficacy of ACI.42	
Vericel	**2.2.3 Need for additional research** The Committee identified a need for additional research. This is surprising as not only is there substantial evidence available, NICE issued positive recommendations on various technologies with much less longer term evidence than is available for ACI. One such precedent is IPG 45643 where suture-less aortic valve replacement was allowed as part of standard NHS procedures based on only short-term evidence (ie a case series of 208 patients and a study with one-year follow-up, while there was some real-world data on one to four year follow-up).	Comment noted. The recommendations have been updated since the Appraisal Consultation Document and there are no longer research recommendations.

Consultee	Comment [sic]	Response
	Another example is TA152 (Drug-eluting stents for the treatment of coronary artery disease2008), which seems to be based on three-year data only, while this is an invasive treatment that can have serious side-effects, yet was approved without the need for further research. 44 Finally there is the example of the anti-TNFs in psoriatic arthritis. Here the three drugs assessed: etanercept, infliximab and adalimumab, only had very limited data on which the assessment was based, namely 24 weeks, 50 weeks and 24 weeks with 12 weeks follow up, respectively. Again this concerns a 13 systemic treatment which carries the risk of (serious) adverse events and had uncertainty about long term efficacy, yet this treatment was allowed without the restriction to research. 45 Similar levels of evidence were deemed sufficient in rheumatoid arthritis. Therefore, given the availability of much longer-term data as described above, Vericel is not convinced that additional data are needed on ACI.	
Vericel	**3 Evidence for Potential Subgroups** **3.1 First-line** Vericel supports the use of ACI as a first-line treatment. In the SUMMIT study, approximately two-thirds of patients did not have a prior therapy, and results were clinically and statistically significant in the full analysis set. In addition, in the approximately one-third of patients who did have a prior therapy, the effect of MACI treatment was still significantly more improved at Year 2 compared with microfracture treatment. *Table3. KOOS Pain and Function in SUMMIT patients at 2 years is not reproduced here. Please see company's response to ACD in the evaluation report* **3.2 Lesion size (>4cm2)** From the published evidence it is clear that the defect size, and especially lesions >4 cm2, is the primary factor predictive of better outcomes when ACI was compared to other techniques (such as MFX).41 This is further	Comment noted. The recommendations have been updated since the Appraisal consultation document was published. The Final Appraisal Determination no longer includes a research recommendation. The committee agreed subgroups based on prior surgery and lesion size should be considered separately.

Consultee	Comment [sic]	Response
	substantiated by published literature which shows that microfracture treatment did worse in 14 lesions than 2cm2. In a direct comparison study of microfracture vs ACI, Knutsen *et al* found in patients with lesions <4 cm2, there was no difference between the two treatments. But in lesions greater than 4 cm2, ACI performed better at 2 and 5 years.46 **3.3 Need for additional research** The Appraisal Committee identified a need for additional research. Vericel respectfully disagrees with this position given the large volume of data that exists on this topic, including randomized, observation studies and academic cohort studies from around the world.	
Vericel	**4 Cost-effectiveness/ efficacy values / second repair/number of people having a TKR/Costs** From the meeting is seems clear that the Committee is not fully convinced of the validity of the Assessment Groups approach and design of the cost-effectiveness model. Vericel shares some of these reservations (eg the utility values from the SUMMIT trial should have been used but were not identified from the systematic review, available longer term data were not used); however, the results were robust to most of the assumptions. All but a few of the sensitivity analyses resulted in ICERs below NICE's threshold. Although it is agreed that there are several uncertainties, for example about practice patterns, several of these could have been explored in more detail through the modelling, in order to better understand their significance. The Committee could have asked for more modelling to be done before deciding that more research is required.	Comments noted. Following the second meeting the assessment group were asked to carry out additional analyses including using alternative utility value assumptions in sensitivity analyses. These additional analyses were considered by the appraisal committee at its third meeting (June 2017).
Vericel	**5 Utility data for ICER** The systematic literature review of the Assessment Group failed to identify the abstract presented at ISPOR of the quality of life data collected alongside the SUMMIT trial. The main publication includes baseline and two-year results using the EQ-5D's visual analogue scale (VAS), (which is not	Comment noted. EQ-5D data from the SUMMIT trial was included in the assessment group's additional analyses and considered by the committee at the third committee meeting (June 2017).

Consultee	Comment [sic]	Response
	the preferred method by NICE. However, in an abstract presented to the 16th European ISPOR Congress, utility values were presented using the EQ-5D questionnaire and the UK tariff.47 As the SUMMIT quality of life data were obtained directly from patients using the EQ-5D, while the Gerlier data used in the model were from an older study, using the SF-36 using a not-described transformation method, the SUMMIT utilities, given that they were available in public domain, should have been used. Results were available for SUMMIT patients at 2 years. The mean utility score for all patients (n=142) at baseline was 0.481±0.296. Responders (n=111) had an improvement in mean utility score from baseline of 0.352 (0.833-0.481) compared with 0.033 for non-responders (n=29; 0.514-0.481) at year 2. Significantly more patients treated with MACI responded to treatment than with MFX (87.5% vs. 68.1%, respectively; p=0.016), resulting in an incremental QALY gain of 0.11 for MACI compared with MFX over 2 years, which is generally viewed by NICE as a relevant increase. These data show that: • At baseline patients have much worse QoL then assumed in the model ie 0.481 vs 0.654 • Responders have a better QoL than in the model 0.833 vs 0.817 15 • Non-responders have a worse QoL than in the model 0.514 vs 0.654 Overall the use of these data in the model would have led to a higher increase in QoL for ACI as compared to MFX and a consequent lowering of the ICER.	
Vericel	**6 Time horizon** Vericel is in agreement with the Committee that the appropriate time horizon of the cost-effectiveness model is lifetime, as changes in mobility affect a person for the remainder of their life. However, we believe that, given the follow-up data presented above it is possible to demonstrate the cost-	Comment noted.

Consultee	Comment [sic]	Response
	effectiveness of MACI without lifetime data, given that the costs of the intervention are at the time of culturing and treatment, and does not involve continuous treatment.	
Vericel	**7 Innovation** Vericel agrees with the Committee that MACI and other ACIs are technically innovative but disagrees with the Committee that ACIs are not innovative in terms of their benefits to patients. Cultured Autologous Chondrocytes should be looked upon as the product that has progressed over time to become safer and more efficient. (M)ACI has had a large societal impact on cartilage (repair) field since 1994. It represents the safest delivery method of providing patients with autologous chondrocyte implantation. The active compound remains the cultured chondrocytes, which provide the durable repair tissue regardless of which generation of delivery is used. Nine Papers with 10 to 20 year follow-up confirm the efficacy, safety and patient satisfaction: • 72 to 85% deemed the procedure Good to Excellent • Average Time to Return to full activity 18 Months (range 12-36mths) • 85% Patient Satisfaction • 80% Patients would have surgery again Therefore Vericel maintains that (M)ACI represents an important innovation to patients. Also, MACI is associated with an improvement on the EQ-5D of more than 0.1, which is normally considered to be an important improvement. References are not reproduced here. Please see company's response to ACD in the evaluation report	Comment noted. The committee agreed that ACI is technically innovative. However, whether additional consideration of innovation is needed in decision making in technology appraisals is dependent on whether there are benefits that have not been captured in the Quality Adjusted Life Years (QALY) calculation. In this case the committee considered that all benefits of ACI would have been captured in this calculation therefore additional consideration of innovation was not warranted (Final Appraisal Determination section 3.25).
BASK	POSITION STATEMENT BY BASK ON THE NICE APPRAISAL CONSULTATION DOCUMENT ON AUTOLOGOUS CHONDROCYTE IMPLANTATION 2015 26 MARCH 2015	Comment noted. The recommendations have been updated since the Appraisal Consultation Document and there are no longer research recommendations.

Consultee	Comment [sic]	Response
	With regard to your Appraisal Consultation Document(ACD) on the MTA (Multiple Technology Appraisal) of Autologous Chondrocyte Implantation (ACI). The British Association for Surgery of the Knee (BASK) would like to respond on behalf of its members and patients. In anticipation of this ACD, BASK discussed ACI in depth at our annual congress in Telford on 10-11th March 2015. The discussion included presentations, open debate, audience voting and an agreement on the position of the BASK with regard to ACI, its evidence base and clinical merit. The conclusion that "Autologous chondrocyte implantation is recommended only in research for repairing symptomatic articular cartilage defects of the knee. Research should include clinical trials and observational studies designed to measure the long-term benefits of autologous chondrocyte implantation" is inconsistent with the evidence already available and has severely detrimental consequences for patients. BASK members note that the committee has misinterpreted the literature and the clinicians view of this technology.	
BASK	BASK would like to contribute the following points to the appraisal: 1. The conclusions of the committee do not appear to be consistent with the evidence available. The committee appear to based their appraisal on the trials set up in response to the 2005 Appraisal and changes in EU licensing, which of course will only have short to mid-term evidence. The committee have interpreted this as a 'lack to long-term data'. There are over 1000 papers in the literature on ACI, including three long-term cohort studies with data on patients over 10 years. These seem to have been ignored by the committee in its conclusions. (see below) 2. Warwick Evidence (commissioned by the HTA programme) concluded that ACI showed a clear benefit over microfracture and mosaicplasty and there was evidence for its use as first-line therapy in appropriate patients.	Comments noted. Following the second committee meeting NICE asked the assessment group to carry out additional searches for long term data (for all generations of ACI and including observational data). These data were considered at the third committee meeting (June 2017). Comment noted. The Appraisal Committee needs to consider the extent of the clinical benefit in order to determine the most plausible

Consultee	Comment [sic]	Response
	The committee seems to have misinterpreted this evidence and stated that the AG group considered the results of their reviews to be inconclusive on the effectiveness of ACI compared to microfracture.	cost effectiveness estimate. The uncertainty arose largely from the biases intrinsic to using different sources of data to the estimate long term comparative effectiveness of ACI and microfracture.
	3. The conclusion of AG is very similar to that of the UK Cartilage Consensus Paper, which is due for publication shortly and has close to 100 signatories of clinicians undertaking care of patients with articular cartilage injury. BASK considers that this is the majority view of experts in this area based on the evidence. BASK also believe that the committee has over-emphasised the views of a single invited expert (who rarely perfoms ACI) whose views do not reflect the majority on the effectiveness of ACI.	The committee considered information in the Consensus Paper in its decision making. The Consensus Paper is referenced in the Final Appraisal Determination.
	4. Warwick Evidence was commissioned by the HTA programme on behalf of the Dept of Health to produce an economic modelling of ACI, which found it to be a cost-effective therapy even at the 'list price' (which none of our members actually pay in the NHS due to procurement discounts). We understand that this economic modelling has itself been independently reviewed and found to be of very high scientific quality. Unfortunately the committee has not accepted this evidence.	Comment noted. The Assessment Group's report followed NICE methods and health technology assessment methods. The uncertainty surrounding the modelled cost effectiveness results arose from limitations in the evidence base and data available for cost effectiveness analyses.
	5. The 'methodological limitations' and criticisms of the RCTs and available studies are used as a basis by the committee to suggest that further research is required. The ACD also refers to "3 small studies". The Genzyme and Tigenix studies were both sufficiently powered to show a difference, and these were large surgical	Comments noted.
	studies. The issues raised with regard to the methodology are actually inherent to this particular clinical situation and cannot be improved. Further research as suggested would not address these issues, are not possible,	

Consultee	Comment [sic]	Response
	and would not provide additional evidence. Furthermore some suggestions by the committee for further research are likely to be unethical. The trials have been assessed using criteria not achievable in surgical trials on this population. Allocation concealment is not possible if one treatment requires a single operation and another requires two operations. Blinding of the surgeon is clearly impossible. Variations in previous treatment are inherent to this population, and reflect the population who would present requiring this surgery. The inclusion criteria for the Chondroselect and MACI RCTs are considered narrow enough to obtain comparable data between the groups and broad enough to include patients who would benefit. Stricter inclusion criteria would render the results applicable to only a very small percentage of patients who might actually present in the clinic. This in itself would be a methodological flaw. 6. With regard to committee concerns about which outcome questionnaires were used, we would comment as follows. BASK agrees that the questionnaires used in early studies were also those used to assess other soft-tissue knee problems and the response to surgery. Although the questionnaires used have evolved over time, they were consistent within studies, and often between studies. Although used for other pathology, all the questionnaires have pain and function reporting which are markers of treatment success or failure in ACI patients. Studies should not be discounted on this issue, and the committee appears to have given this matter too much emphasis in their evaluation of data. 7. With reference to section 5.4. “The Committee heard that the clinical experts differed with respect to how effective they perceived ACI to be compared with microfracture. The committee heard that this may in part reflect a clinician’s experience and preference. When asked to judge the clinical effectiveness of ACI, clinical experts stated that there was some evidence to show that ACI is clinically effective, but also stated that this evidence was not	The discussion of the symptom scoring systems used in the trials has been deleted from the Final Appraisal Determination. This is because it was no longer considered a key consideration in the committee’s decision making. The text has been updated since the Appraisal Consultation document following additional analyses from the assessment group and discussions at the second and third committee meeting. The committee were aware of the Consensus Paper and took this into account in its decision making at the third meeting.

Consultee	Comment [sic]	Response
	definitive. They also stated that, although ACI, microfracture, and mosaicplasty were probably clinically effective, evidence was lacking for the natural history of lesions treated by debridement and lavage". BASK disagree. This is absolutely not the clinical situation or the view of the majority of knee surgeons. The views of one "clinician expert", without sound evidence seem to carry more weight than would be merited. ACI has a very strong evidence base for safety and efficacy in worldwide clinical practise, it is not merely dependent on one doctor's personal experience. We would consider the evidence definitive. The natural history of untreated large articular cartilage lesions is osteoarthritis. This is beyond doubt. Two of the clinical experts present confirmed this. It is possible that a view that a single clinician "expert" who gave written and verbal opinions has skewed the committee into believing there was vast difference of opinion within the orthopaedic community In fact there is not. Based on the views expressed at the recent BASK congress and those signing the UK Cartilage Consensus statements the majority view of those who undertake cartilage repair surgery is that ACI is safe, effective, and superior to comparators in many situations. 8. With regard to the AG evaluation of the effectiveness of ACI, and the committee concern that the AG favoured inappropriately. The AG view of this is justified by reference to the long-term cohort studies and the RCT of ACI vs Mosaicplasty at 10 years by Bentley 2012, which demonstrate enduring results with ACI even in unfavourable large multi-operated knees. Other papers which support our view are: Minas T et al Clin Orthop Relat Res. 2014 Jan;472(1):41-51. Biant LC et al Am J Sports Med. 2014;42(9):2178-83. Peterson L et al Am J Sports Med. 2010 Jun;38(6):1117-24. 9. The recommendations of the committee for further research is misguided with regard to this appraisal. Suggesting that an RCT should be done against physiotherapy, sham surgery or debridement alone implies a	Comment noted. Comment noted. The recommendations have been updated and the Final Appraisal

Consultee	Comment [sic]	Response
	misunderstanding of the indication for surgery in the first place. All patients considered for ACI will have had physiotherapy and failure of conservative treatment, and nearly all will have had an arthroscopic debridement and lavage and further physiotherapy before ACI is considered. We believe, once again that, the unsubstantiated opinion of one clinician has been weighted too heavily. An RCT against physio alone is not reasonable as all these patients have already failed conservative treatment. An RCT against debridement alone is not reasonable as most of the patients will have already failed this before ACI would be considered. An RCT against sham surgery could be deemed unethical, as most patients will already have had a failure of debridement.	Determination no longer includes a research recommendation.
BASK	Other considerations for the Committee are important for patients: 1. In large lesions, ACI is the ONLY proven therapy that is effective. Even those who advocate microfracture acknowledge that microfracture should not be performed in lesions over 2cm. Furthermore, doing ACI as second line after failed microfracture renders the patient with a less favourable outcome than if ACI done first. NICE is about to deny NHS patients the only effective treatment for their pathology. 2. No further research is likely to be funded by industry or grant-awarding bodies, as this is established treatment that has been in practice for over 25 years. Good research exists, funding of further research will not be forthcoming. NICE Committee interpretation of available literature exhibits a misunderstanding of the clinical situation. 3. NICE research suggestions are entirely inappropriate to our patients. 4. Suggesting ACI only in the context of further research is not a safe or pragmatic compromise option. It will effectively kill the technique in the UK and significantly disadvantage our patients. Moreover, it will set back	Comments noted. The recommendations have been updated since the ACD and ACI is now recommended for lesions over 2 cm^2 and as a first treatment.

Consultee	Comment [sic]	Response
	healthcare in regenerative orthopaedics back 25 years instead of facilitating responsible innovation. BASK members believe that ACI should be publically funded on the NHS for appropriate patients who have failed conservative treatment. Collection of outcome data could be mandated. The International Cartilage Repair Society has a registry in progress. Centralising services in a small number of centres regionally is sensible and reduces overall cost.	
British Orthopaedic Association	The conclusion reached in the Appraisal Consultation Document (ACD) on the Multiple Technology Appraisal of ACI is flawed and detrimental to good patient care for a number of reasons. Since the last appraisal in 2005 a number of trials which had already started before 2005 have now provided the evidence for the efficacy of ACI as a treatment for isolated chondral defects of the knee. Not only have they reported the success of this methodology but also the cost effectiveness. The evidence from Warwick has shown what we as clinicians already know, namely that ACI produces superior results for patients in terms of pain relief when compared to microfracture and mosaicplasty not only in the short-term but also into the medium to long-term. It has been suggested that the review of the literature is inconclusive but this is not the case. The literature for ACI is more compelling and better evidenced than microfracture especially for the larger defects. There are over 1000 relevant papers in the literature and long-term studies with patient data in excess of 10 years. Further the efficacy of microfracture declines after 5 years. ACI works and is cost effective and whilst we accept that there is more work to be done in this area to define further the patients who gain the most from this technology, it would not be in patients best interests to deny them this treatment pathway when appropriate. We would recommend that NICE supports this treatment and it is provided through NHS funding. We would recommend and support that all patients continue to be placed into observational studies and the availability of this	Comments noted. Following the second committee meeting NICE asked the assessment group to carry out additional searches for long term data (for all generations of ACI and including observational data). These data were considered at the third committee meeting. The committee concluded at the third meeting that it had seen the best available data for its decision making. It took these data and all comments received from patient and clinical experts into account in its decision making.

Consultee	Comment [sic]	Response
	treatment pathway be restricted to centres who use this technology in at least 50 patients per annum. Where it is felt appropriate for patients to receive ACI, after informed consent and appropriate discussion, the treatment costs must be met by the relevant CCG. Failure to allow appropriate patients access to this technology through the NHS funding route will condemn them to a life of on-going pain and progressive joint degeneration, leading to early joint replacement and the need for expensive revision surgery. The National Clinical Reference Group for Specialist Orthopaedics have already looked into this technology and support its use. The British Orthopaedic Association is the voice of trauma and orthopaedic care in the UK. It supports its members but more importantly is there to ensure the highest standards and availability of care for all patients who undergo operative procedures. It is perhaps unfortunate that an invited "clinician expert" views were given more weight than perhaps appropriate when in fact their clinical experience and publication record in the field of ACI is limited. In future the BOA would be happy to work with NICE to identify appropriate "experts" to provide informed well balanced opinions on matters or technologies deemed to be within the remit of trauma and orthopaedics.	

Comments received from clinical specialists and patient experts

Nominating organisation	Comment [sic]	Response
BASK	Comments on the ACD of Autologous chondrocyte implantation for repairing symptomatic articular cartilage defects of the knee. The consultation document above 1. Has not taken into account all of the relevant evidence 2. Has not appropriately interpreted the evidence 3. The provisional guidance is entirely unsound 4. The suggestions for further research are inappropriate and unethical	Comments noted. The responses to the comments are provided as they are raised individually below.

Nominating organisation	Comment [sic]	Response
BASK	Errors in ACD 2.7 and 5.3 “There are no UK guidelines or internationally accepted treatment on how to treat cartilage lesions” The Committee was provided with the UK Cartilage Consensus Paper, which is in press. It is due to be published in April 2015. It had 72 signatories of clinicians involved in cartilage repair in the UK at the time it was submitted to NICE. It now has close to 100, which represents the majority of orthopaedic surgeons who perform this durgery. The Dutch Orthopaedic Society and the German Orthopaedic Society have previously published similar papers. One of the reasons the UK Cartilage Consensus Meeting was convened, was due to the previous NICE Appraisal being cited by NHS and other health providers to deny patients access to treatments where the clinicians consider the evidence to be strong enough to recommend ACI in appropriate patients. There is considerable variation in access to these services across the UK. Furthermore, clinicians were concerned that doing comparator treatments such as microfracture is less effective and compromises the chances of subsequent repair with ACI.	Comment noted. At the third committee meeting the consensus in this paper was discussed and used by the committee in its decision making. A reference to the paper has been added to the Final Appraisal Determination document.
BASK	4.1. The Committee’s summary of the AG review of clinical evidence demonstrates miniterpretation of the AGs evidence. First generation ACI (ACI-P) has a higher rate of patch hypertrophy which is amenable to correction by day-case arthroscopy, but there is no higher failure rate of the repair itself. There are comparative trials of different forms of ACI which show no difference in clinical result. The AG stated CONCLUSIVELY from their review that ACI was more effective than microfracture.	Comments noted. The Final Appraisal Determination now states that there is some evidence that ACI works better than microfracture in the short term. The uncertainties surrounding the extent of this, and whether ACI works better than microfracture in the long term are discussed in the Final Appraisal Determination.

Nominating organisation	Comment [sic]	Response
BASK	4.6 The summary suggests that the AG regard the TIG/ACT trials as good quality. This is true. “However, the AG regards ACI-P as obsolete”. This implies that the trial is now irrelevant to the current therapy. This is a misinterpretation of the AG evidence and the clinical situation. ACI-P uses a different patch than ACI-C or MACI. The repair is just as good with ACI-P, as stated in the AG addendum, but the small complication of patch hypertrophy is much less in ACI-C and MACI, which is one reason they are favoured now. The trial is of relevance and should not be discounted or considered less valuable on these grounds. In fact, any evidence from this study is that shows the superiority of ACI over microfracture is likely to be greater with ACI-C or MACI, as stated in the AG report. There is no difference in the re-operation rate between ACI-C and ACI-P in the ACTIVE trial *Table not reproduced here*	Comments noted. Following the second committee meeting the assessment group included data from all generations of ACI in a new analysis.
BASK	5.2 “The Committee did not consider best supportive care (including physiotherapy) to be a relevant comparator because the Committee heard that best supportive care had already failed by the time clinicians consider ACI” 6.3 “Further research is recommended to compare ACI, mosaicplasty and microfracture with conservative treatment” The ACD contradicts itself entirely here. It was explained that surgeons do not consider surgery unless conservative methods have failed. It is therefore illogical, if not unethical to recommend research against a comparator treatment the patient has already failed by the time the present to the clinician and the Committee	Comments noted. The recommendations have been updated since the Appraisal Consultation Document and there are no longer research recommendations.

Nominating organisation	Comment [sic]	Response
BASK	5.3 “It (The Committee) noted 3 small studies with relatively short follow-up” These studies are not small surgical studies, and should not be benchmarked against drug studies. The studies mentioned are adequately powered, appropriate and methodologically sound enough to show a difference between ACI and microfracture. Indeed they all have, even at ‘relatively short follow-up”. If longer follow-up evidence is required, there are cohort studies and an RCT against mosaicplasty with data at minimum 10 years, and a total of 15 RCTs involving ACI. *Table not reproduced here*	Comment noted. The wording has been updated since the appraisal consultation document. Additional longer term studies (RCTs and observational studies) were considered by the assessment group in its additional analyses carried out after the second committee meeting
BASK	5.3 “Lysholm, Tegner and Cincinnatic scores were not regularly used in clinical practice and some were of limited relevance to the general population with cartilage defects”. This is a misinterpretation of what the clinician experts reported. These measures were used in cartilage repair patients in earlier studies before articular cartilage-specific scores were developed. The Lysholm Score has been validated in patients with chondral lesions (Kocher MS et al JBJS Am 2004). They were used for general soft-tissue knee problems including meniscal damage or ligament damage and reflect pain and function in an active population (as opposed to an elderly arthritis population). They are reasonable measures of pain and function and allow intra-study comparison between treatments and comparison between studies.	Comment noted. The discussion of the symptom scoring systems used in the trials has been deleted from the Final Appraisal Determination. This is because it was no longer considered a key consideration in the committee’s decision making.

Nominating organisation	Comment [sic]	Response
BASK	5.4 “The Committee heard that the clinical experts differed with respect to how effective they perceived ACI to be compared with microfracture. The Committee heard that this may in part reflect a clinician’s experience and preference. When asked to judge the clinical effectiveness of ACI, clinical experts stated that there was some evidence to show that ACI is clinically effective, but also stated that the evidence was not definitive. They also stated that, although ACI, microfracture, and mosaicplasty were probably clinically effective, evidence was lacking for the natural history of lesions treated by debridement and lavage”. This is absolutely not what the clinicians expressed. It was the stated opinion of one of the clinicians present, not the other two who were given insufficient opportunity to respond, because one had to leave part-way through the meeting (having been invited at too short notice to cancel a clinic) and because the other was part of the AG, who are not invited to make any presentation. The one clinician is not representative of the vast majority of surgeons who perform this surgery, and who have put their signatures to the UK cartilage Consensus Paper. The Committee may have given too much weight to the opinion of one, who was in contradiction to the majority of surgeons, the evidence in the literature and the AG. The evidence for ACI is solid and multiple, and irrespective or preference and experience and is absolutely definitive. Around 100 clinicians have signed the UK Cartilage Consensus Paper. “They also stated that there was evidence lacking for the natural history of lesions treated by debridement and lavage”.	Comments noted. The text has been updated since the Appraisal Consultation document following additional analyses from the assessment group and discussions at the second and third committee meeting. The committee were aware of the Consensus Paper and took this into account in its decision making at the third meeting.

Nominating organisation	Comment [sic]	Response
BASK	5.5 “The Committee noted that it was presented with no clinical effectiveness data beyond 5 years” and “insufficient long-term evidence to support a conclusion on the long-term effectiveness of ACI” This data is available, and the Committee should avail itself of this. The AG or two of the clinical experts could have presented this had they been asked.	Comment noted. The assessment group were asked by NICE to carry out additional searches for long term data. At the third meeting the committee were satisfied that they had seen the best available data for estimating long term clinical effectiveness of ACI.
BASK	5.7 “It (the Committee) noted that the claimed advantages of ACI over microfracture in its use for larger lesions was not supported by the study of Minas and colleagues (2009)” The paper by Minas has been misinterpreted entirely by the Committee, and the paper in fact has evidence exactly to the contrary	Comment noted. This statement is not in the Final Appraisal Determination.
BASK	5.8 and 5.10 “significant uncertainty in the cost-effectiveness results” (of the AG) I know as co-author of the assessment report that the economic modelling of the AG has been independently assessed for quality and has been deemed to be of very good academic quality with a score of 5/6 by an independent referee chosen by the HTA programme editors.	Comment noted. This statement was not a criticism of the assessment group’s analyses or modelling. It reflected the data limitations and the resulting uncertainty in the modelling.
BASK	6.3 “ Further research is recommended to compare ACI, mosaicplasty and microfracture with conservative treatment, for example, sham (placebo) procedure, lavage and debridement, or intensive physiotherapy that reflects the rehabilitation following ACI” This is illogical, and likely unethical. The Committee itself has already stated that conservative measures are an inappropriate comparator in section 5.2 “The Committee did not consider best supportive care (including physiotherapy) to be a relevant comparator because the Committee heard that best supportive care had already been failed by the time clinicians consider ACI”	Comment noted. The recommendations have changed since the Appraisal Consultation Document was issued and there are no longer research recommendations.

Nominating organisation	Comment [sic]	Response
BASK	NICE has not taken into account all the available evidence and has not accurately interpreted the evidence presented to it. The guidance is inappropriate and will deny effective treatment to patients, based on their flawed interpretation of clinical effectiveness data. The Committee was, perhaps, also inappropriately influenced by a clinician who did not represent the majority view, nor a sound evidence base for his statements.	Comment noted. The recommendations have been updated following consideration of additional analyses from the assessment group, which were requested from the Appraisal Committee at its second meeting in April 2015 (when it discussed these consultation comments).

Comments received from commentators

Commentator	Comment [sic]	Response
Catapault	OUR COMMENT: "Cell therapies have the potential to deliver long-term benefits to the patient and the healthcare system; however long-term value claims can be compromised when the available clinical evidence is of a shorter term (as in the case of ACI). The NICE DSU support document 14, (March 2013) describes a number of methods for performing extrapolations with patient-level data and emphasizes the importance of assessing the plausibility of extrapolated data through clinical expert opinion and biological plausibility in conjunction with sensitivity analysis. We believe there is a need for clarification about how clinical opinion and biological plausibility are factored alongside the survival analysis modelling methods described so that manufacturers are better guided in substantiating long-term claims. Furthermore genuine risk-sharing mechanisms (rather than mere discounts) could both encourage innovation and mitigate risk for both the healthcare system and the manufacturers. We suggest a risk-sharing/patient access scheme is considered in the case of ACI".	Comments noted. Following the second committee meeting at the request of the Appraisal Committee the assessment group carried out additional analyses including further extrapolations from patient level data and sensitivity analyses. The plausibility of extrapolations is taken into account by the committee through a deliberative process, alongside other uncertainties surrounding the data. The Appraisal Committee or NICE cannot initiate patient access schemes.

	1. Section 4.5 on TIG/ACT trial. The results show no significant differences overall and there were more adverse events in the ChondroCelect group. There were better results for ChondroCelect patients with a symptom history shorter than 3 years, but the natural history of chondral lesions is not well documented so these patients might have experienced symptomatic improvement even without treatment.	Comment noted.
	2. Section 4.7. Same comments apply to an uncontrolled report of use of ChondroCelect in patients with chondral defects. No control group, limited documentation of natural history of these lesions makes results difficult to interpret.	Comment noted.
	3. However it is worth pointing out that in the assessment report considered in the meeting of February 10th the assessment document contains the information "Three case series (refs 34-36) reported high levels of return to activities after cartilage injuries after 14 year, 9 years and 9 years respectively" and this refers to patients who had no cartilage surgical procedure. In one of these studies Maletius reported a case series of young athletes (mean age 25, range 14-38) who had no treatment. Fourteen years later, most (21 out of 28) had returned to activity and 22 had excellent or good function. The assumption that patients with chondral lesions have a poor prognosis is not borne out by this literature although I would concede the data is limited.	Comment noted.
	4. Section 4.10. The MACI product is not currently available on the European market as the parent company have closed the Danish laboratory that was providing the product. 5. In section 4.15 there is a commentary on the ACTIVE trial. This trial showed no difference in the first 4 years between the ACI and	Comment noted. The Final Appraisal Determination states that NICE recommendations only apply to technologies with a marketing authorisation for cartilage defects of the knee.

	microfracture groups. There was a difference in favour of ACI at 5 years. However I would point out that the number of patients with this duration of follow-up would be relatively small. We were told during the February 10th meeting that the reason for the long duration of time before benefit was observed was that the cartilage matrix took this long to regenerate. This however would not be consistent with other trials and case series that report favourable symptomatic responses at 6 – 12 months. I do not understand how it can plausibly be argued that one trial would indicate it takes over 4 years for ACI to regenerate the cartilaginous matrix and other trials show benefit within 2 years. Both cannot be correct?	Comments noted. All available trial data and differences were taken into account by the Appraisal Committee.
	6. There are other inconsistencies in the literature. Bentley et al in 2012 reported the 10 year results of ACI vs mosaicplasty with a failure rate of 17% at 10 years in the ACI group. This was a trial involving in 100 patients. However in 2014, from the same unit as the trial with some of the same authors the failure rate of a much larger case series of 827 patients with a failure rate at 10 years of 50%. Same unit, same surgery, same surgeons – and a radically different outcome in a much larger series of patients. How do we interpret this?	Comments noted. All available study data, differences between studies and uncertainties were taken into account by the committee and are described in the Final Appraisal Determination.
	7. In section 4.21 we are told the economic model estimates the cost of cell harvest at £722.45 and the cost of the implantation procedure at £109.65. I am not sure how these figures are derived but the cost estimate of cell implantation seems likely to be wrong. The cell harvest procedure is a minor quick arthroscopic procedure whereas the reimplantation is a longer procedure most often performed as an open procedure. I fail to understand how this more complex procedure is estimated to cost little more than a seventh of the more minor harvesting operation. I would also disagree that failure after	Comments noted. These costs were those proposed by the company who produced the ChondroCelect model. The committee's preferred costs were the from Healthcare Resource Group codes that is, £870 for harvesting and £2396 for implantation (section 3.18 of the Final Appraisal Determination).

	microfracture would be followed by a further microfracture procedure. I would say that most surgeons would be inclined not to attempt a repeat of a procedure which has already failed and would opt to either continue nonoperative treatment or perhaps offer an osteotomy. 8. I would therefore disagree with the statement in 4.22 that "the economic model in the ChondroCelect submission was logical, and was backed by mostly plausible assumptions". The statement "it was reasonable to assume that microfracture is the only relevant comparator for ACI" ignores the fact that many surgeons might choose to offer patients mosaicplasty as an alternative. 9. In section 4.25 we are asked to believe ACI is more cost effective than microfracture with no difference in the first 4 years of the ACTIVE trial between the 2 treatments and based on less than 30 patients in each treatment arm with longer term follow-up. This is not a conclusion based on robust data. 10. In section 5.5 there is a reasonable summary of the discussion regarding short and longer term outcomes after ACI. However the explanation that that ACI takes longer to become effective because the cartilaginous matrix takes longer to develop is not consistent with some studies showing early benefit. What is the explanation for this? A sceptical explanation might be that the procedure is of little value	Comment noted. The marketing authorisation for ChondroCelect was withdrawn between the second and third committee meeting and the committee used the assessment group's model for its decision making (Final Appraisal Determination section 3.14). The use of mosaicplasty and microfracture were further considered in subsequent meetings. Both were considered comparators but microfracture was considered the most relevant for decision making because the committee heard microfracture is the most commonly used treatment in the absence of ACI. Comment noted. The limitations of the available data to make a robust comparison between ACI and microfracture are discussed in sections 3.6 to 3.12. Comment noted.

Commentator	Comment [sic]	Response
	and early benefit can be attributed to a placebo effect and the late improvement is due to the variation in symptoms associated with the natural history of chondral lesions where symptoms commonly wax and wane over time. 11. Section 5.14 “literature-based estimates of the rates of knee replacement surgery vary widely in people with cartilage damage”. True but the fact remains that the requirement of TKR in the UK population overall is 0.1% so the risk of requiring TKR is low. 12. Section 5.23. This conclusion is a good summary of the status of ACI at the present time. It should only be used in the NHS in well-designed clinical trials that are likely to confirm or refute its efficacy in the treatment of symptomatic chondral defects in the knee. In the following section on key conclusions I have no amendments to suggest.	Comment noted. Comment noted. The recommendations were updated following the committee’s consideration of the draft recommendation in the Appraisal Consultation Document and additional analyses provided by the assessment group following the second committee meeting. It was determined that taking into account the uncertainties surrounding the data that there were some groups in which ACI was likely to be cost effective, and as such should be recommended for the people outlined in section 1.1 of the Final Appraisal Determination.

Comments received from members of the public

Role*	Section	Comment [sic]	Response

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Health Professional	All	Dear NICE committee members It is with respect for the amount of detail and impressed by the width of the topic covered that I have studied your preliminary document and the committee papers. As one of the leading authors of publications evaluated in your work and past president of the International Cartilage Repair Society (ICRS) I feel we have a combined responsibility to ensure proper conclusions are made and final position is described. It is of paramount importance that not only the UK healthcare, clinical, strategical or financial drivers in this judgement are considered but that one also appreciates how NICE guidance is viewed by other regulatory bodies and insurance carriers in the EU and elsewhere. Hoping to further improve the final document and help reach a correct status and create a pathway forward I have chosen to provide some suggestions and comments. These merit consideration and would help make refinements in some essential aspects of the text and choice to be made. Ad 1.1 Since ACI using the MACI and ChondroCelect products are both registered as ATMP under EMA regulations and EU law and have thus passed all requirements for standard clinical implementation we should refrain from using wording such as experimental and in research only. ACI has a long standing well established history and from the first generation techniques longterm follow up has been published which shows longterm efficacy of over 13 years average and more than 20 years outcomes. The preliminary wording in 1.1 should be changed to allow implementation in standard care using broadly accepted treatment algorithm applicable to the local situation and selected centers for cases with high complexity and	Comment noted. The responses are given below to each raised issue. The recommendations have been updated following consideration of additional analyses from the assessment group, which were requested from the Appraisal Committee at its second meeting in April 2015 (when it discussed these consultation comments). There is no longer a research recommendation.

		additional needs. Proposed wording: — Autologous chondrocyte implantation is recommended for repairing symptomatic articular cartilage defects of the knee. Compulsory nationwide registration of use, adverse effects and efficacy is mandatory and regular reporting to the EMA advised. Observational studies and registry input should be designed to confirm the long-term clinical and economic benefits of autologous chondrocyte implantation. ACI should be used according to the UK national guidelines as developed and published by the committee of professionals and subscribed to by over 100 active experts in the field Ad 2.4 There is a typing error or serious mistake in the microfracture indication in section 2.4. This now reads Microfracture is normally used for lesion sizes of less than 13 cm2. This is incorrect and should read Proposed wording: 1-3 cm2. Since Mfx is absolutely not prefered for larger defects. Mosaicplasty (also known as osteochondral transplantation) involves transplanting small sections of cartilage and underlying bone from a less weight-bearing part of the knee into the damaged area. Mosaicplasty is used for small areas of damage (less than 4 cm2). This is not common practice since 4 cm is considered a large defect size and donor site morbidity in the less weight bearing area would be unacceptable. Thus if used at all Mosaicplasty is currently applied to osteochondral defects in which 1-2 plugs can completely fill the symptomatic defect.	Comment noted. The committee referred to the consensus paper of UK knee surgeons in its decision making at the third committee meeting. Comment noted. This statement is not in the Final Appraisal Determination. Comments noted. The Appraisal Committee took into account that ACI is considered the only effective option for cartilage defects over 2 cm^2 (Final Appraisal Determination section 3.1).

		Proposed wording : Mosaicplasty can be used for small areas of damage (less than 2 cm2) and is indicated mainly for osteochondral lesions. Ad 2.5 Biopsies are not only take from the less weight bearing region if such exists. Literature and common practice have established biopsy from the defect rim as effective as well as using the vital cartilage from the loose body present in some ACI indications. EMA regulation for the EU dictates that any ATMP and thus all ACI products are required to include a GMP/GCP compliant process including viability/potency/efficacy markers. Thus patients, providers, policymakers and payers are assured that the transplanted cells have and over 95% viability and cartilage repair potency. Proposed wording: ACI involves taking a biopsy of cartilage from the affected knee during arthroscopic surgery. Chondrocytes from the cartilage are then cultured in a laboratory to increase their number. Cultured expansion should abide by GMP/GCP compliant EMA regulation and include viability, potency initial efficacy biomarkers. Finally, the chondrocytes are implanted into the area of damaged cartilage during a second surgical procedure using a biological or biomaterial cover with proper fixation to allow for cell attachment.. ACI is not indicated for degenerative arthritic joints. Ad 2.7: There is a well performed UK consensus treatment guideline which has active support of over 100 expert professionals in the clinical field. In addition national treatment guidelines, therapy advice or consensus statements have been published and are in use for Belgium, The Netherlands, Germany, Spain and the United States of America.	Comment noted. Section 2.5 is not in the Final Appraisal Determination (the template for Appraisal Consultation Documents and Final Appraisal Determinations has changed since the Appraisal Consultation Document for this appraisal was published, and no longer includes a background section). The Final Appraisal Determination states in the new table in section 2 that “ACI is contraindicated in people with severe osteoarthritis of the knee”. Comment noted. The consensus paper of UK Knee surgeons has been referenced in the Final Appraisal Determination.

		Proposed wording: There are well described UK guidelines and internationally accepted treatment algorithms on how and when to treat cartilage lesions. Cartilage repair treatment should be selected for individual patients according current the most up to date UK published consensus. Ad 4.1 The conclusion described in this section is unfair, simplistic and does not do justice to the rigorous investigation and increasing quality of studies published in this innovative field for which methodology is still being developed. Traditional RCT guidelines and Pharma based methodology cannot be simply be applied to surgical investigations of ATMP and cell therapy. Comparator selection is debatable, samples size calculations are correct and thus study size cannot be deemed small if the predefined statistical analysis plan was correct and followed. Then conclusions are valid. Also one must remember in the initial statement 200-500 patients annually in the UK are expected thus trials including 120-150 patients are considered to be adequate and for randomized surgical trials even large. Lack of allocation concealment is impossible in surgical comparison of such various techniques, and does not fit within needs for informed consent. Patient reported outcomes are used for clinical efficacy thus blinding of assessment scoring is not realistic. The two largest regulatory submission approved trials for ChondroCelent and for MACI have been peer reviewed and published in the highest impact factor journals in this field, awarded best international research in the field by the largest scientific society, accepted as proof of structural superiority as well as clinical superiority by EMA and thus provide acceptable evidence to conclude that ACI comparable or better than microfracture and mosaicplasty and can be the preferred method of treatment in selected patients.	Comments noted. The summary of the clinical trial data and assessment group's critique of the randomized controlled trials (sections 4.1 to 4.18 of the Appraisal Consultation Document) is no longer reported in the Final Appraisal Determination and readers are directed to the committee papers to read the full assessment group report and company submissions. The committee's consideration of the clinical effectiveness evidence is presented in sections 3.5 to 3.13 of the Final Appraisal Determination.

		Proposed wording: Therefore the Assessment Group considered the effectiveness of ACI to be comparable or better when compared with microfracture for larger size defects. Ad 4.2 Agree with summary and propose only one point which needs change to reflect literature and professional interpretation ï‚· People with small lesions had better outcomes with microfracture than people with bigger lesions. ï‚· Among people with larger lesions, ACI appeared to produce better outcomes compared with microfracture. Ad 4.6 The primary outcome of the TigACT trial was structural superiority on histological analysis and clinical non inferiority at 1 year on overall KOOS. This was met and the trial showed significantly better tissue structure from ACI than after Mfx. With subsequent predefined clinical PROMs evaluation at 5 years we were able to show durability of the repair and the significant better outcome in patients treated earlier. This being the first trial and first registered ATMP in a then still undeveloped field must be remembered when we now judge studies designed in 2000 and from which we have learned much and improved both subsequent trials and clinical treatments. The use of words such as obsolete is inappropriate and taint the paragraph as if the treatment and trial results were obsolete which is not the case. Also the use of periosteal cover although not preferred is still a viable option and n the USA even imperative since the synthetic collagen covers are not registered there yet.	

		Proposed wording: The use of ChondroCelect after the TIG/ACT study was registered including a synthetic cover because periosteum has no obvious clinical advantages over second or third generation ACI, needs more time in surgery, and is associated with higher subsequent costs (for example, shaving of hypertrophy). Ad 5.3 Final sentence is derogatory to current evidence and decennia of clinical outcomes and satisfied patients. As time, technology and treatment application progress clearly evidence and supportive data will be emerging. That by no means should infer that current proof is insufficient for implementation of ACI in NHS care. One could even argue that it would be unethical not to provide that EMA approved EU registered clinically successful and when implemented correctly cost effective therapy to a wider patient population. Why would patients be further studied or have been randomized if only the resulting convincing science were to be blocked by scientifically framed economical objections. Ad 5.4 The there mentioned experts should be presented differently since only one person was of that opinion on many aspects of the questions now generalized in the preliminary report. Thus it would be better either to query a larger group of experts on exactly these aspects or to not over exemplify the personal opinion of one older surgeon out of touch with this specific field. Ad 5.5 As previously mentioned and even discussed in the NICE prelim document the comm was aware and presented with long term data of very robust evidence supporting the long term efficacy of ACI. Both in the Minas data as in the Petterson data this is well described and should not be disregarded in this summary. Given all previous arguments and altered wording the final sentence of this	Comment noted. The recommendations have been updated since the Appraisal Consultation Document and the Final Appraisal Determination no longer includes a research recommendation. Comments noted. The Final Appraisal Determination references the Consensus Paper of 104 UK knee surgeons and the committee took into account this paper in its decision making. Comments noted. Following the consultation comments on the Appraisal Consultation Document and the second committee meeting (when these comments were discussed), the Appraisal Committee requested further analyses of the long term clinical

		section should be altered. Proposed wording: Since there was extensive relevant additional data on the effectiveness of ACI since the previous guidance on the use of autologous chondrocyte implantation for the treatment of cartilage defects in the knee joints, the previosuly exsisting shortcomings associated with the medium-term evidence and insufficient long-term evidence to support a conclusion on the long-term effectiveness of ACI have been addressed and thus ACI can be considered using the UK treatment algorithm within the requirement of a prospective nationwide registry. Ad 5.6 EMA guidance and EU regulation dictated that clinicians are only allowed to use ATMP registered cell therapy products. This has nothing to do with personal preference and treatment choice but is part of European law ! Thus this section needs to be altered since now it reads as if the group is unaware of these essential aspects. Ad 5.21 given the previous arguments and obvious clinical improvement from ACI as well as the many innovations in subsequent technology this section should be changed. It is beyond any reasonable doubt that ACI is proven technology and that it comprises a very visible innovation in healthcare. Two of the three currently registered ATMPs are cartilage cell therapy products. And innovation is not judged by the number of people affected but by a larger societal impact such as ACI has had on RM field since 1994 and continues to have. A recent Nature publication deemed ACI to be a clear and highly innovative example of Technovolution and thus should be considered for all intents and purposes in this document innovative, effective and established.	effectiveness studies by the assessment group, including observational data. The committee took these additional analyses into account in its third meeting. Comments noted. The Final Appraisal Determination section 3.3 states “The committee concluded that it was relevant to consider all the data on clinical and cost effectiveness it had received. However, its recommendations would apply only to technologies with a current marketing authorisation or an MHRA hospital exemption from the regulation on advanced therapy medicinal products.” The equivalent to section 5.21 in the Appraisal consultation document (section 3.25 in the Final Appraisal Determination) states that ACI is innovative, but it does not meet the NICE method’s guide criteria for additional consideration of innovation by the Appraisal Committee in its decision making.

Role*	Section	Comment [sic]	Response
		Ad 5.23 Given all previous suggestions and the obvious need for a considerable adaptation of the final document to represent scientific and clinical reality properly we now need to re address this final paragraph. Proposed wording: The Committee therefore recommended that, because the clinical effectiveness has ben established, cost-effectiveness of ACI as applied in a well defined treatment algorithm has bee demonstrated and patient numbers for this indication are limited in the UK to 200-500 with marginal financial impact, ACI should be recommended for use in the NHS when applied following current UK consensus indications and as part of a compulsory prospective national registry. The Committee noted that these studies should generate robust outcome data and include both interventional and observational studies. Ad summary tables: due to the considerable changes proposed and the impact of such on the whole document I feel detailed comments on the final tables summary has no beneficial role at this point. These should clearly be revised once the full document refinement has been completed. Hoping this adds to the overall quality of the effort and of the final result, I remain respectfully available for input and questions as wells as interested in the further alterations and result of this important proceedings.	Comment noted. The recommendation has been updated since the Appraisal Consultation Document was issued. Comment noted. NICE Appraisal Consultation Documents and Final Appraisal Determination no longer include summary tables

Health Professional (NHS)	All	In my view the overview conclusion statement: 'Autologous chondrocyte implantation is recommended only in research for repairing symptomatic articular cartilage defects of the knee' is not justified by the evidence available and the evidence considered in the document. There has been inappropriate interpretation of the evidence and the views of knee specialists who have experience and who have knowledge of the treatment have not been adequately considered. There is now clear evidence from well powered clinical trials that ACI is better than the comparator microfracture and has a clear indication in specific situations. In addition there is clear evidence that the result of ACI when performed AFTER microfracture is worse with much lower success rate. This is mentioned in the document but not acted on. ACI should therefore be allowed as a primary treatment when indicated. There are very few patients who actually need the treatment as it is indicated in failed conservative treatment (rehabilitation) and lesions on one surface of the joint larger than 2cm square. 200 - 500 a year is a small number but a very relevant number. The data shows that quality of life and health economics can be improved by proven treatment. Specific Comments: 2.7: There are now UK guidelines produced as a consensus document by UK surgeons. This was submitted to NICE but is not referred to. I am one of the lead 4 authors on that paper. OVER 95 SPECIALIST KNEE SURGEONS HAVE AGREED WITH THE CONSENSUS DOCUMENT.	Comments noted. The recommendations have been updated since the Appraisal Consultation Document was issued. Comment noted. The Consensus Paper of 104 UK knee surgeons was taken into account by the committee and is referenced in the Final Appraisal Determination.

		"ADDITIONAL COMMENTS ON THE REPORT 3.3: cost of treatment: The cost of chondrocelect to the NHS is NOT £18,301 - it is nearer £11,000. The figure of 18K over dramaticises the cost of this effective treatment 4.2: Brilliant summary - so why not allow use of ACI? Section 4.7 onward - The Trials evidence: it is acknowledged in the document that the TIG/ACT trial showed better results that microfracture, and that the SUMMIT trial also showed better results for ACI. These are both well powered and well resourced studies done to the best scientific methodology that can be funded in the current day. Why would the document ignore these findings and still want more studies before recommending use of the ACI technology as primary treatment? In 4.18 the document acknowledges: The Assessment Group stated that the evidence is limited by the evolving nature of the technology, and because the longest-term data come from early versions of ACI that have largely been superseded. The Assessment Group stated that most, but not all, studies suggest that ACI is more effective than microfracture if it is used soon after the cartilage injury. How long do we have to wait for the evidence to be accepted that ACI is a better treatment?? In 4.22 and in 4.24 the document argues in favour of cost effectiveness. This is not acted on in the conclusion. In 4.36 after long analysis it is stated ACI provided greater gain in QALY. In 5.3 The Committee concluded that, although there is more clinical-effectiveness data than at the time of the previous NICE technology appraisal guidance on the use of ACI for the treatment	Comment noted. The Final Appraisal Determination notes the uncertainty surrounding cell costs and states the cost on which the decision was based (section 3.19) Comments noted. The summary of the clinical trial data and assessment group's critique of the randomized controlled trials (sections 4.1 to 4.18 of the Appraisal Consultation Document) is no longer reported in the Final Appraisal Determination and readers are directed to the committee papers to read the full assessment group report and company submissions. The committee's consideration of the clinical effectiveness evidence is presented in sections 3.5 to 3.13 of the Final Appraisal Determination.

		of cartilage defects in the knee joints, the evidence base for the technology is still emerging . The Committee has commented that the RCT's were small - yet in knee surgery terms these are big, well powered and well funded. They cannot be downplayed. It was stated that the evidence base is still emerging - yes it is but the evidence NOW is very strong. The Committee has made inappropriate interpretation of the evidence summarised. In 5.4 The Committee heard that the clinical experts differed with respect to how effective they perceived ACI to be compared with microfracture. The Committee heard that this may in part reflect a clinician™s experience and preference. When asked to judge the clinical effectiveness of ACI, clinical experts stated that there was some evidence to show that ACI is clinically effective, but also stated that this evidence was not definitive. They also stated that, although ACI, microfracture, and mosaicplasty were probably clinically effective, evidence was lacking for the natural history of lesions treated by debridement and lavage It is innappropriate to base a review on published trial evidence and then take the personal view of one surgeon who says something about his own personal view - when he has never used the technology. The 95 surgeons agreeing the consensus document feel otherwise. In 5.7 It (The Committee) noted that the claimed advantages of ACI over microfracture in its use for larger lesions was not supported by the study of Minas and colleagues (2009) This is an entirely wrong conclusion of that paper - the content of which should be read.	Comment noted. The Final Appraisal Document does not state that the evidence base is still emerging. Comment noted. The Consensus Paper of 104 UK knee surgeons was taken into account by the committee and is referenced in the Final Appraisal Determination.

Role*	Section	Comment [sic]	Response
		In 6.3. Further research is recommended to compare ACI, mosaiclasty and microfracture with conservative treatment, for example, sham (placebo) procedure, lavage and debridement, or intensive physiotherapy that reflects the rehabilitation following ACI There is so much evidence so far that cell treatment is effective that such a trial would be difficult to recruit to and it would be hard for a surgeon to have equipoise MORE COMMENTS IN NEXT SECTION " "FINAL COMMENTS TO GO WITH PREVIOUS COMMENT DOCUMENT The conclusion section seems to go against all the positive evidence presented. The Committee indicates it was not persuaded - it should need to be persuaded as the scientific data in conclusive as mentioned in the analysis. Lastly the Committee wants more observational studies in the future: yet the whole conclusion part belittles the data as it is. How can observation studies every provide the answer this Committee wants?? ACI should be funded and then trials as to how to optimise indications and how to improve outcome should be recommended The consensus document contains all these suggestions. Thank you for reading and considering this	This statement has not been included in the Final Appraisal Determination. The recommendations have been updated since the Appraisal Consultation Document and the Final Appraisal Determination does not include a research recommendation.

Healthcare industry	All	The comments herein are made on behalf of The International Cartilage Repair Society (ICRS) on request from and with approval of The ICRS Executive Committee. The ICRS is a forum for international collaboration in cartilaginous tissue research by bringing together basic scientists and clinical researchers engaged or interested in the field of cartilage biology: http://www.cartilage.org General comment We wish to state categorically that the overview conclusion statement: 'Autologous chondrocyte implantation is recommended only in research for repairing symptomatic articular cartilage defects of the knee' cannot be justified in light of the available evidence. There is very clear evidence from properly powered clinical trials that ACI is better than the comparator microfracture and that ACI has a clear indication in specific situations. It is also clear that the result of ACI when performed AFTER microfracture is worse, with much lower success rate. Whilst this is mentioned in the NICE document, it does not appear to have been taken into account. Specific comments 1. There are over 1000 papers in the literature on ACI, including three long-term cohort studies with data on patients over 10 years. These seem to have been ignored by the committee in its conclusions. 2. Warwick Evidence (commissioned by the HTA programme) concluded that ACI showed a clear benefit over microfracture and mosaicplasty and there was evidence for its use as first-line therapy in appropriate patients. This conclusion is very similar to that of the UK Cartilage Consensus Paper, which is due for publication shortly	Comment noted. The recommendations have been updated since the Appraisal Consultation Document was issued. The recommendations take into account better outcomes and an increased likelihood of cost effectiveness when ACI is the first surgical treatment used for cartilage defects of the knee. Comments noted. The committee took into account all data included from the assessment group's systematic review and the company submissions in the committee papers. It also asked for a further review and analyses to be carried out by the assessment group after the second committee meeting. The Consensus paper has been referenced in the Final Appraisal Determination.

		and has close to 100 signatories of clinicians undertaking care of patients with articular cartilage injury. ICRS considers that conclusion reflects view of the majority of experts in this are. Warwick Evidence was commissioned by the HTA programme on behalf of the Dept of Health to produce an economic modelling of ACI, which found it to be a cost-effective therapy. 3. The ACD refers to 3 small studies . It is worth noting however that the Genzyme and Tigenix studies were both sufficiently powered to show a difference, and these cannot be considered as small in the context of orthopaedic surgical studies. We do not believe that the further research suggested would provide any useful evidence beyond that already published. The committee has suggested that future clinical trial design would be improved by allocation concealment. However this is not possible in this situation as one treatment (microfracture or osteochondral grafting) requires a single operation and the other (ACI) requires two operations. Blinding of the surgeon is not possible. 4. Sustained long-term beneficial results of ACI have been reported in several studies that have not been taken properly into account by the committee. These include: Minas T et al Clin Orthop Relat Res. 2014 Jan;472(1):41-51. Biant LC et al Am J Sports Med. 2014;42(9):2178-83. Peterson L et al Am J Sports Med. 2010 Jun;38(6):1117-24. Bentley G et al J Bone Joint Surg Br. 2012 Apr;94(4):504-9. Moseley JB Jr et al Am J Sports Med. 2010 38(2):238-46. Conclusions	Comments noted. Comments noted.

Role*	Section	Comment [sic]	Response
		On behalf of ICRS we request that NICE re-examines the available data taking into full account all of the published studies. There also needs to be careful re-examination of the proposed additional research that is needed as it appears to have been proposed with no real understanding of the design limitations in surgical clinical trials in general and cartilage repair surgery in particular.	The recommendations have been updated since the Appraisal Consultation Document was issued.

Healthcare provessional (private)		I have been working with cartilage repair for almost 30 years and in basic science as well as in clinical research and practice. I have been using autologous chondrocyte implantation for patients since Lars Peterson and I did the first ACI in October 1987 in Gothenburg with cells cultured by Professor Anders Lindahl. It is with great interest I have read the comprehensive consultation document. I have some comments to the text, please see below. 1 Appraisal Committee™s preliminary recommendations 1.1 Autologous chondrocyte implantation is recommended only in research for repairing symptomatic articular cartilage defects of the knee. Research should include clinical trials and observational studies designed to measure the long-term benefits of autologous chondrocyte implantation. Comments: Autologous Chondrocyte implantation was first introduced to the world in October 1987 by our group in Gothenburg (Lars Peterson, Mats Brittberg, Anders Lindahl). Since then several thousands of patients have been operated with that method all over the world. From the first generation of ACI with cells injected as a suspension in under a periosteal membrane to second generation of ACI with cells under a collagen membrane to now 3rd generation ACI with cells seeded on or in matrices. The ACI technology has further been evaluated in the last 10 years with 15 different randomized studies. Eleven of those studies have been ACI versus another repair technique. In 7/11 of those studies, ACI showed a significant superiority over the other technique. Seven of the studies were ACI versus microfracture (MFX) and of those studies ACI was significantly better in different parameters than MFX in 5/7. There are not many other orthopaedic techniques that have been so thoroughly examined. To conclude that ACI should only be used in	Comments noted. Comments noted. The recommendations have been updated since the Appraisal Consultation Document was issued.

		research would then mean that most other orthopaedic operations should only be used in research meaning that also when using MFX it should also be only as a research project. As with all different operative treatments, ACI should be used with care and ACI as well as other cartilage repair treatment should be monitored in registries (national and/or international).Today, there are two ACI technologies that have been approved by EMEA. I suggest that in the text it should be noted that the approved ACI technologies are used as per their indications while other ACI variants are used in research studies until being approved by EMEA. 2.4 .Microfracture involves drilling small holes through the bone under the damaged cartilage to allow bone marrow cells to fill the damaged area and to differentiate into chondrocytes Comments: Microfracture is not drilling but a perforation of the subchondral bone plate to reach intracortical vessels. The resulting bleeding is developed into a blood clot that functions as a scaffold to attract cells from the bone marrow. Such cells could be mesenchymal stem cells that may go into a chondrogeneic lineage producing a fibrocartilaginous tissue repair. However, it is not that they become pure chondrocytes. 2.4Microfracture is normally used for lesion sizes of less than 13 cm2. Comments: Microfracture is normally used for lesion sizes of less than 3cm2!	Comment noted. Sections 2.4 and 2.5 are not in the Final Appraisal Determination (the template for Appraisal Consultation Documents and Final Appraisal Determinations has changed since the Appraisal Consultation Document for this appraisal was published, and no longer includes a background section).

		2.5.Finally, the chondrocytes are implanted into the area of damaged Cartilage during a second surgical procedure, in the hope that they will repair the damaged area. Comments: The wording ¨in the hope that they will repair¨is not suitable as it is a degree of subjectivity from the evaluator which means that the evaluator not fully believes that the cells are involved in the repair. It is not written similarly regarding the other techniques but a certain degree of hope is also involved in those repairs.. 2.4 .Microfracture involves drilling small holes through the bone under the damaged cartilage to allow bone marrow cells to fill the damaged area and to differentiate into chondrocytes Comments: Microfracture is not drilling but a perforation of the subchondral bone plate to reach intracortical vessels. The resulting bleeding is developed into a blood clot that functions as a scaffold to attract cells from the bone marrow. Such cells could be mesenchymal stem cells that may go into a chondrogeneic lineage producing a fibrocartilaginous tissue repair. However, it is not that they become pure chondrocytes. 2.4Microfracture is normally used for lesion sizes of less than 13 cm2. Comments: Microfracture is normally used for lesion sizes of less than 3cm2!	

		2.5.Finally, the chondrocytes are implanted into the area of damaged Cartilage during a second surgical procedure, in the hope that they will repair the damaged area. Comments: The wording ¨in the hope that they will repair¨is not suitable as it is a degree of subjectivity from the evaluator which means that the evaluator not fully believes that the cells are involved in the repair. It is not written similarly regarding the other techniques but a certain degree of hope is also involved in those repairs.. 5.3: . The Committee further concluded that, although there is more clinical-effectiveness data than at the time of the previous NICE technology appraisal guidance on the use of autologous chondrocyte implantation for the treatment of cartilage defects in the knee joints, the evidence base for the technology is still emerging. Comments: However, on section 4.18 The Assessment Group stated that most, but not all, studies suggest that ACI is more effective than microfracture if it is used soon after the cartilage injury.Is there then enough evidence to use microfracture instead of ACI ? The evidence base of that MFX technology and all other cartilage repair is also still emerging. Recently, research has shown that deep drilling may be a better alternative than mfx. 5:16: confidential discounts sometimes provided to the NHS by the companies, making the real cost difficult to evaluate. Comments: As the costs presented in the committee report not illustrate the actual reality costs, the calculations are of less value.	Comment noted.

		Remember that ACI is mostly used as a secondary procedure after that other cartilage repair methods have failed. To make a new secondary or a third surgery that may fail is very expensive and could be a catastrophe for the patient. 5:22: .The Committee therefore recommended that, because the clinical effectiveness and cost-effectiveness of ACI remains uncertain, ACI should not be recommended for routine use in the NHS unless it is part of existing or new clinical studies... Comments: In my practice, patients are referred to me due to several failed cartilage repair operations. Such patients are difficult to treat but ACI is in such occasions a possible solution. Most of the reports in the literature are on patients getting an ACI after failed other surgeries and there are long term results up to 20 years follow up. In patient treatments, there are responders and non “responders and the amount of studies retrospective, prospective and randomized that have been done with ACI has shown that ACI has a clinical effectiveness with long time duration in this severe patient category. If based on the committees evaluation, ACI should only be done as part of existing or new clinical studies, all other cartilage repair methods should also be done only as part of clinical studies.Engen et al. found that Knee cartilage defect patients enrolled in randomized controlled trials are not representative of patients in orthopaedic practice. For a fair use of different repair methods in the future, all cartilage repairs could be followed in arthroscopy registers like what is already done in ACL registers in the Scandinavian countries. I believe it will be easier to get the true clinical effectiveness of different methods in such register follow ups related to all methods whatever costs they present.	Comment noted. The committee took into account the uncertainty surrounding cell costs in its decision making. Final Appraisal Determination section 3.19. Comments noted. The recommendations have been updated since the Appraisal Consultation Document was issued. The Final Appraisal Determination no longer includes a research recommendation.

Role*	Section	Comment [sic]	Response
		I hope my comments may be of help for the final conclusions of the use of ACI as well as of other repair methods.Sincerely Yours,	

Healthcare professional (private)	All	I have been working with cartilage repair in Japan. I have read the documents and I have several comments to the review team™s conclusion as follows. 1.1 Autologous chondrocyte implantation is recommended only in research for repairing symptomatic articular cartilage defects of the knee. Research should include clinical trials and observational studies designed to measure the long-term benefits of autologous chondrocyte implantation. 5:22: .The Committee therefore recommended that, because the clinical effectiveness and cost-effectiveness of ACI remains uncertain, ACI should not be recommended for routine use in the NHS unless it is part of existing or new clinical studies... Comments: There have been over 10 comparative studies of ACI versus microfracture (MF). It is notable that most recent studies (Crawford JBJS 2012, Saris Am J Sports Med 2014) showed significantly better subjective outcomes by ACI as compared with MF. This means well designed RCTs could delineate the advantage of ACI over MF and thus it is too early to conclude that ACI should only be used in research although the significance of ACI still needs be proved by future studies. 2.4 .Microfracture involves drilling small holes through the bone under the damaged cartilage to allow bone marrow cells to fill the damaged area and to differentiate into chondrocytes Comments: It should be noted that MF procedure could develop postoperative subchondral bone pathology such as intralesional osteophyte (Minas, Am J Sports Med 2009, Cole, Am J Sports Med 2011) and thus might not be regarded as benign procedure as has been recognized. As could be the case with autologous	Comments noted. Comment noted. Sections 2.4 and 2.5 are not in the Final Appraisal Determination (the template for Appraisal Consultation Documents and Final Appraisal Determinations has changed since the Appraisal Consultation Document for this

		osteochondral plug implantation such as mosaic plasty and OATs, these procedures require the sacrifice of healthy cartilage (donor site) with equivalent size to the lesion and there have been several reports regarding the donor-site morbidity associated with the procedures (Sagstetter, J Bone Joint Surg Am 2009, Kock, Acta Orthop 2010). Likewise, this procedure might not be a benign intervention and we should not easily draw a conclusion regarding this procedure, either. In this regard, ACI procedure which does not damage subchondral bone could have theoretical advantage and thus, once again, we may need precisely to followup the patients after all the intervention available now including ACI and other options and it is too early to conclude that ACI should only be used in research. 2.5.Finally, the chondrocytes are implanted into the area of damaged Cartilage during a second surgical procedure, in the hope that they will repair the damaged area. Comments: The wording ¨in the hope that they will repair¨is not suitable as it is a degree of subjectivity from the evaluator which means that the evaluator not fully believes that the cells are involved in the repair. It is not written similarly regarding the other techniques but a certain degree of hope is also involved in those repairs.. I hope my comments may be of help for the final conclusions of the use of ACI as well as of other repair methods. Sincerely Yours,	appraisal was published, and no longer includes a background section).

Role*	Section	Comment [sic]	Response

Healthcare professional (NHS)	All	Options for biological repair have been available for 20 years. Yet despite this, and multiple sources citing better response with biological reconstruction, NICE deems it necessary to still classify this as "Experimental". The majority of patients who have treatable lesions have no access to such treatment on the NHS. It would appear that the current recommendations would like symptomatic patients to remain symptomatic until eventual irreversible, mutilating arthroplasty, unless they are fortunate enough to be in proximity to a research establishment. Estimating that the annual treatable portion of the population to be 200 or so is clearly a gross underestimate based on data from a period when MRIs are not as frequent as today. Costs of such treatment do not take into consideration that economies of scale mean the costs would decline as the therapy becomes mainstream. This guidance needs to be updated annually, such is the rapidity of new technologies entering the market. One example is the single stage stem cell application treatment. i.e. the Shetty Kim technique. This enhanced Microfracture using concentrated stem cells is a procedure that has an additional cost of only £1000, and has already proved effective up to 3 years from implantation. In my humble opinion, NICE should accept that this is no longer experimental study after 20 years of treatments. Guidance should be concentrating on advising on patient selection, based around long term health economic analysis. Would recommend the establishment of a Cartilage Registry in the UK, much the same way as the NJR to provide advice ad evidence	Comment noted. The recommendations have been updated since the Appraisal Consultation Document was issued. The Final Appraisal Determination does not include a research recommendation. The Appraisal Committee took into account uncertainties surrounding the costs of cells in its decision making and the Final Appraisal Consultation states the cost on which the recommendation is based (Final Appraisal Determination section 3.19)

Role*	Section	Comment [sic]	Response
		that responds to the evolution of the technology in agile responsive way. I am happy to develop one if needed.	
Healthcare research	All	I am surprised and bewildered that NICE should conclude from the abundant evidence in its own report: 'Autologous chondrocyte implantation for repairing symptomatic articular cartilage defects of the knee (including a review of TA89)' that ACI is not yet sufficiently demonstrated to show long term benefits and cost effectiveness to approve its adoption as an intervention. As a scientist involved in basic research into knee biomechanics and research for patient benefit into pre- and re-habilitation for debilitating knee articular cartilage defects, and being myself a patient suffering from this condition, I am on the contrary convinced by this evidence that ACI both as a first intervention and for reintervention is a more appropriate procedure than microfracture, which is known to damage subchondral bone, and creates an biomechanically inappropriate fibrocartilage layer, which cannot by definition perform the lubrication functions of hyaline cartilage required at the knee, and which fibrocartilage layer has a short lifetime. The evidence is already there in this report that ACI is the better approach, which damages subchondral bone less and produces a biomechanically appropriate and long-lasting hyaline cartilage repair. Requiring further research which is most unlikely to get funded, particularly in the current research funding environment, will unnecessarily prolong implementation of a viable intervention for another decade, and thus prolog suffering of patients for no good reason.	Comments noted. The recommendations have been updated since the appraisal consultation document was issued and the Final Appraisal Consultation no longer includes a research recommendation.

Role*	Section	Comment [sic]	Response
Healthcare professional (NHS)	All	I do not consider that the appraisal consultation document reflects the true state of treatments for chondral defects. Whilst evidence was gathered it has not been taken into account of in a scientifically robust method. There is good evidence for the use of ACI. There are prospective randomised trials which have shown clear benefits and economic analyses have shown that this treatment is cost effective. The trials were adequately powered and with adequate follow-up. in 6.3 the report states that 'further research is recommended to compare ACI, mosaicplasty and micro fracture with conservative treatment, for example , sham (placebo) procedure, lavage and debridement, or intensive physiotherapy that reflects the rehabilitation following ACI.' This follows the committee stating in 5.2 that conservative measures are an inappropriate comparator. Mosaicplasty has fallen into disrepute as it damages other areas of the knee and fails to restore a congruent chondral surface. Microfracture is inappropriate for large lesions. ACI should be a first line treatment. This document disadvantages young patients who need chondral surfaces reconstructed to allow them to lead a normal life at home and in leisure time. UK patients have been disadvantaged following the previous NICE guidance where ACI was deemed to be experimental. Whilst stem cell therapies may be developed they are not proven either scientifically or economically.	Comments noted. The recommendations have been updated since the appraisal consultation document was issued and the Final Appraisal Consultation no longer includes a research recommendation.

Healthcare professional (NHS)	All	You state that there are no UK or International guidelines on how to treat cartilage lesions however there are in the form of the UK Cartilage consensus paper. This supports use of ACI as a primary procedure for lesions over 2 sq cm and this is based on good long term evidence. You have commissioned your own independent Appraisal guidance and I feel you have misinterpreted the results as it quite clearly shows that not only is ACI effective it is also cost effective. This is also based on good quality evidence. ACI as shown by the Appraisal group has been shown to be cost effective using the list price of products. You have not taken into account that almost no users will pay this price, as they will receive substantial discounts, dependant on volume of use. As a result ACI will be more cost effective than you have demonstrated. I understand that you have heard evidence from one clinician who stated that there is doubt about the efficacy of ACI. I believe that this one opinion does not concur with the vast majority of surgeons who are up to date with ACI techniques and the literature surrounding its use. This is evidenced by the large number signing the UK Cartilage consensus paper. NICE suggest more research is required, I feel that there is enough evidence to show that it has already been demonstrated to be an effective treatment. As such it is likely that no further research will be funded and this valuable technique will simply fall into disuse. If this occurs then NICE will be responsible for denying patients a well supported proven, cost effective treatment. It is likely if treatment is denied then patients will receive a lesser treatment with poorer	Comments noted. The UK Cartilage consensus paper is referenced in the Final Appraisal Determination and was taken into account by the Appraisal Committee. ACI is now recommended as a primary procedure for lesions over 2 cm^2. The uncertainty surrounding the cost of cells is discussed in section 3.19 of the Final Appraisal Determination.

Role*	Section	Comment [sic]	Response
		outcome or will be asked to contact NICE directly to ask what they should do in lieu of receiving no treatment.	
Healthcare professional (NHS)	All	It seems incredible to me that despite years now of thorough investigation and an excellent body of robust evidence that cartilage implantation is not recommended in day to day practice. The evidence presented to the NICE committee and recommendations by the UK consensus group must be upheld if we are to continue to look after the best interests of our patients. Cartilage implantation is not universally applicable, but where it is indicated as per the evidence, it should be recommended by NICE as first line therapy.	Comment noted. The recommendations have been updated since the Appraisal Consultation Document was issued.
Healthcare professional (NHS)	All	Dear Sirs, I do not feel all the evidence has been appropriately taken into account as all my reading and experience surrounding this treatment clearly shows better efficacy in the medium term than any other treatment for this difficult group of patients. Handcuffing this to further research which is already exhaustive will ultimately have the opposite effect and result in withdrawal of chondrocyte therapies for our generation.	Comment noted. The recommendations have been updated since the Appraisal Consultation Document issued. The Final Appraisal Determination no longer includes a research recommendation.

Role*	Section	Comment [sic]	Response
Healthcare professional (NHS)	All	As a knee surgeon, I see a large number of patients with chondral pathologies who would benefit from ACI treatment. Unfortunately there is no other alternative treatment available for young patients with large chondral defects. There is enough available evidence in literature suggesting clinical and cost effectiveness of ACI type treatments. I was hoping that after many years of wait, I would finally be allowed to offer this treatment to selected patients who have no other hope for their knee pathology. This TA review has restored status quo and would do a disservice to a large group of patients. Unfortunately, there is no other new treatment on horizon. If NICE is concerned about cost implications, use of this technology can be restricted to larger centres, with patients being referred to such centres.	Comment noted. The recommendations have been updated since the Appraisal Consultation Document was issued.
Healthcare professional (NHS)	All	Usual stupidity. The knee community jumps through hoops to prove that something works and then it is still turned down. How many more young people are going to have to suffer before we are allowed to use something that works and is cost effective? please change the guidance and allow this treatment	Comment noted. The recommendations have been updated since the Appraisal Consultation Document was issued.
Healthcare professional (NHS)	All	I believe that the evidence is fairly convincing that, for isolated contained cartilage defects in stable knees, the best quality cartilage with sustained functional improvement is achieved by ACI. This should no longer be termed "experimental" as the evidence is abundant and good quality.	Comment noted. The recommendations have been updated since the Appraisal Consultation Document issued. The Final Appraisal Determination no longer includes a research recommendation.

Role*	Section	Comment [sic]	Response
Healthcare professional (NHS)	All	Autologous Chondrocyte Implantation is an important technique that can restore articular cartilage to an injured knee. This will allow pain relief and restored function to a largely young patient group. It may delay or avoid the need for more extensive surgery such as arthroplasty. There is a strong evidence base to support it's use , but the continued collection of data, and multicentre controlled trials are very important. I strongly urge NICE to asupport the continued practice and development of ACI therapies. Not doing so would significantly disadvantage a generation of young sufferers, and would severely damage an area of clinical research in which the UK currently is one of the leaders	Comment noted. The recommendations have been updated since the Appraisal Consultation Document issued.
Healthcare professional (NHS)	All	I am bemuse dat teh conclusion that this procedure has nothing to offer. We are desperately in need of biological solutions to biological problems. Bits of metal and plastic only do so much. The young and active need better solutions and in ACI we have one such. The evidence in support of it is clear. I do not understand how the conclusions have been reached.	Comment noted. The recommendations have been updated since the Appraisal Consultation Document issued.

Role*	Section	Comment [sic]	Response
Healthcare professional (NHS)	All	It is disappointing that despite the evidence of a Consensus Paper submitted and supported by the majority of UK orthopaedic surgeons involved in treating chondral lesions, the committee still consider there to be insufficient evidence to support the use of ACI. Our EU partners disagree with the findings of your committee and have approved the use ACI technologies for treating chondral lesions for several years now, so much so that is has proved difficult to recruit patients into any further randomised studies comparing ACI with micro fracture. Sufficient evidence exists in the literature to support the superiority of ACI. (Basad et al KSSTA 2010, Van Lauwe et al AJSM 2011, Cole et al AJSM 2011, Crawford et al JBJS (Am) 2012, Saris et al AJSM 2014.)	Comment noted. The recommendations have been updated since the Appraisal Consultation Document issued.
Healthcare professional (NHS)	All	This procedure has an enormous amount of data over several decades. In selected cases (large defects in young patients with stable, well-aligned knees & menisci intact / replaced) the evidence is very strong that this is not experimental, but should be recommended as primary treatment.	Comment noted. The recommendations have been updated since the Appraisal Consultation Document issued. The Final Appraisal Determination no longer includes a research recommendation.
Healthcare professional (NHS)	All	I disagree with the recommendations made using the available evidence that NICE has at its disposal. The evidence for ACI is compelling and only offering micro fracture instead of ACI is unethical with the evidence we have.	Comment noted. The recommendations have been updated since the Appraisal Consultation Document issued.

Role*	Section	Comment [sic]	Response
Healthcare professional (NHS)	All	I have been in practice as a consultant in knee surgery for over 30 years and I have lectured in knee surgery in Australia, Brazil, Canada, Chile, China, Equador, Egypt, Greece, India, Italy, Peru, Portugal, Singapore and Zambia and operated in Egypt. I am well aware of the merits of ACI and firmly believe that in the correct hands this should now be an accepted procedure for use in the primary situation.	Comment noted. The recommendations have been updated since the Appraisal Consultation Document issued.
Healthcare professional (NHS)	All	I am unclear why the appraisal does not support ACI, when independent review of the literature by the Warwick group gave support and advised ACI was an appropriate treatment , clinically effective and economically value for money.	Comment noted. The recommendations have been updated since the Appraisal Consultation Document issued.
Healthcare professional (NHS)	All	Having read the assessment report prepared by Warwick evidence and the draft appraisal consultation document, I would like to share my views. There is good quality evidence that demonstrates that ACI should be recommended (shown good long term results), including for use as a first line treatment . The evidence also uses the list price for ACI products, thus the actual cost benefits will be greater than quoted as most hospitals will receive discount on their ACI products. Whilst I agree that results and patient outcomes should be audited I disagree that further "research" is required, as there is already a good level of evidence to support its use. It is unlikely that any further funding for such research will be granted, for what is considered by most to be of proven therapeutic benefit.	Comment noted. The recommendations have been updated since the Appraisal Consultation Document issued.
Healthcare professional (NHS)	All	This document is short sighted and ill informed. It ignores a wealth of good quality research within this field. Whilst ACI is not a panacea it is has it's place in the arthritis prevention options available to surgeons.	Comment noted. The recommendations have been updated since the Appraisal Consultation Document issued.

Role*	Section	Comment [sic]	Response
Healthcare professional (NHS)	All	As a retired knee surgeon practicing for over 30 years I found the research and clinical evidence for this procedure compelling. The number of patients in my practice with cartilage defects for whom I felt it was indicated was relatively small, so I referred patients on to surgeons with considerable experience of the technique. This is no longer a research procedure, but should be part of the standard surgical procedures for repair of cartilage defects	Comment noted. The recommendations have been updated since the Appraisal Consultation Document issued.
Healthcare professional (Private)	All	i had done around 60 ACI/MACI as a member of Stanmore trial between 2002-2010, both NHS and BMI HIGHFIELD private hospitals. there was 60 -70% good results. Tibio-femoral joint was better than Patello/femoral one.A lot of young people were delighted with results. ACI transformed lifes of so many people.	Comment noted. The recommendations have been updated since the Appraisal Consultation Document issued.

Autologous Chondrocyte Implantation Cartilage Repair

Comments from Patients who have undergone treatment

Submitted to BASK January/February 2016

Surgeons undertaking ACI contacted patients who had undergone ACI/MACI/CCI treatment inviting submission of comments by email to BASK at NICE@cartilage-repair.co.uk

Over 30 patients responded in 4 weeks

Comments attached in Date order, compiled into single document

21st Feb 2016

E-mail from [redacted]: MACI graft

To NICE@cartilagerepair.co.uk
Dear Sirs

In May 2013, I underwent surgery to perform a MACI graft on my right knee and I write in full support of the continuing use of this treatment.

For many years I have been actively involved in sport, mainly running, having been a member of my local athletics club from an early age. I developed chronic pain in the right knee which meant that I could no longer run or cycle, struggled to walk up and downstairs, couldn't effectively bend the knee or kneel down and had constant pain when sitting for long periods or driving. Bring a quantity surveyor by profession, this also affected my work .

A MRI scan showed some abnormality in the cartilage but during an arthroscopy, it was found that a piece of cartilage roughly the size of a two pence piece had disintegrated. This was too large to be repaired by microfracture technique.

My consultant ([redacted]) suggested a MACI graft and this was accepted by my health insurers. The procedure was undertaken March to May 2013 followed by a year of rehabilitation.

The operation transformed the knee and my general wellbeing. The post operative aching gradually disappeared and I have been able to resume an active, healthy lifestyle competing in triathlon and other events. My day to day lifestyle is also much improved as I no longer struggle to walk up and downstairs, the constant aching on sitting has gone and gradually, my ability to bend and kneel down has much improved.

Without this operation my quality of life would be much reduced at what is a relatively young age (51) and I would fully support the continued use of this technique to give others the same opportunity afforded to me.

Yours sincerely

[redacted]

E-mail from [redacted]: Autologous Chondrocyte Implantation

[redacted]

[redacted]pair.co.uk

Dear Sir/Madam,

I wish to write in the strongest terms of support for the procedure of Autologous Chondrocyte Implantation.

At the age of 47 my knees decided that they would no longer allow me to exercise vigorously and within a short period of time, no exercise at all. I began to put on weight and mentally struggled with the absence of exercise.

By the age of 50 I was becoming unable to walk up stairs in a "normal" fashion and had to drag one leg after the other because the pain was too great. Everyday functionality became limited and I would not stand or walk if I could avoid it. I had to purchase an automatic car.

At the age of 50 I had the first of my ACI procedures and within four months I was walking up stairs normally again and was virtually pain free. Within six months of the procedure I went skiing for the first time in my life.Less than three years later it was necessary to have the same procedure on the right knee as it was failing in the same fashion as the left.

Before the procedures:

my life was not in any sense normal as mobility and willingness to be mobile was very limited. The pain was too great. This was leading to bad general health conditions such as moderate obesity and a frustration because of that inability to move and the total absence of exercise.

After the procedures:

My life returned to as **normal** a state as possible, walking normally with complete freedom and absence of pain, moderate exercise from time to time and an absence of feeling "imprisoned" Now at the age of 60, I conduct a full working life and anticipate that I will continue to do so for another twenty years, God willing.

Why did i elect for this surgery instead of knee replacement?

It is the only logical risk managed approach.

If it failed I still had my own knees - likely to be in better condition than before although I would have been the subject of at least 4 surgical procedures when bilateral, (two arthroscopies & two arthrotomies)

Despite statistical analysis, I encounter a lot of people who are not in any way ambivalent when they state that their prosthetic knee procedure has been a failure in their eyes. This has certainly been the case within my own family. There is no way back from prosthetic knee surgery. By adopting ACI, I retained prostheses in reserve.

At the age of my first procedure, 50, there would have been considerable resistance to giving me a prosthesis as it would be considered certain that I would need another procedure and possibly another before I died. I undertook the surgeries when I was young enough to withstand them.

Observations

If ACI was integrated at a much earlier appropriate lifestage such as when my knee pathologies first began to develop at 31, I consider that it is possible that subsequent knee pathologies and surgeries could have been avoided.

In the strongest possible terms, I unequivocally recommend that ACI should become a standard procedure within the NHS.

Yours faithfully,

[redacted]

FW: Support for NICE review of Cartilage repair surgery

Fro [redacted]
Sent: [redacted]
To:
Subject: RE: Support for NICE review of Cartilage repair surgery

Dear NICE

I was treated at the Nuffield in Leamington in February 2012. This followed an arthroscopy that showed that I had very little remaining cartilage on my left knee as a result of 20 years of playing cricket, football and skiing. The knee was causing significant pain and limiting my ability to play even gentle sports such as golf.

Four years on, I am back playing golf, cricket and have also taken up tennis. I don't have the constant pain in my knee that I lived with previously.

My expectations was set that the operation would give me pain free movement but I have been very pleased that I have been able to resume a level of sport that I did not anticipate before the operation.

Please let me know if you need anything further.

Regards,

[redacted]

[redacted] : MACI

[redacted]

To nice@cartilagerepair.co.uk
To Whom it concerns,

Pre surgery I had extensive wear to the joint surfaces as my Meniscus was practically non - existent. I ruled out walking any distance other than into the shops due to the pain and swelling that would follow (at age 29)

[redacted]

I then visited [redacted] and the conclusion of the meeting was that I need the MACI graft, Meniscal allograft and an ACL reconstruction. (Biological knee replacement)

The surgery (Nov 2012) was extensive and the recovery was long and slow but now at age 33 I can walk without pain, stand at work (I work as a service engineer in hospitals) before I was looking for a seat constantly. I am now cycling 8hrs per week at a competitive amateur level. I now feel that I have a knee for the future that I feel confident in. I can also now run without pain but choose not to, to preserve my new knee.

I hope that you can make this surgery a choice for those that are suitable.

Regards,

[redacted]

E-mail from [redacted] Support for NICE review of Cartilage repair surgery

[redacted]

To whom it may concern,

On the 31st Aug 2014 I had a repair done to the articular cartilage on the lower surface of my right femur using the ACI technique. The size of the damaged area was very large - 5-6 cm2. Too large for other operations such as OATS.

Before the operation I had pain when standing from sitting which would take considerable time to stop. (pain level 6/10) Walking up stairs was painful (7/10) and I was not able to run (10/10). I could not live a good quality of life without being able to do these things. Having one child at the time, I needed to be able to kick a football around in the back garden. With the pain at the time this was not possible.

Since having the operation I am back to all the sports I enjoyed earlier in my life. I can row for up to 2 hrs without pain. I Can squat heavy weights in the gym. Running is coming back gradually - although I am taking this high impact exercise very very slowly for obvious reasons.I can now chase my son should he run away from me which is important for his safety and my peace of mind.

My quality of life has improved immeasurably. I am positive and feel 20 years younger and not like a decrepit old man. I am able to go for long walks with family and friends and at work as a teacher I can change from sitting down to walking around the class frequently and feel no pain.

Without the ACI technique I would be probably staring a full knee replacement earlier in my life than I should need, if ever.

[redacted]

E-mail from [redacted]: Testimonial - private

Dear Sir/ madam,

I have been made aware by my consultant that you are collecting testimonials in relation to the benefits of the operation to repair articular cartilage in knees. Not being an expert I simply refer to the operation as the MACI operation. I have benefitted twice from this procedure (my right knee in 2013 and my left knee last year (2015)). Before having the operation/s my knees were sore, felt unstable (in the sense that I was very concerned that they could give way at any time) and would occasionally lock and click in a disturbing manner. Collectively the symptoms were really quite debilitating with the prospect that they would get worse and the medium term likelihood that I would develop arthritis.

The treatment to each of my knees has corrected all of the symptoms, it is true that the nerve damage to my knees as a result of the operations leaves a slightly strange sensation, but apart from that it has given my a new lease of life. My pain has gone, I feel my knees are structurally sound and I have averted the medium term likelihood of painful arthritis. The operations have changed my life and I can now play properly with my two girls (aged 10 and 4). Without the operations I would not enjoy the quality of life that I have now in many areas of life. Most important, as mentioned, is my family life but I can now actively participate in sport (which is important to me) and engage in all sorts of activities which, until you have the symptoms caused by cartilage damage, you cannot imagine.

I cannot express enough how much this procedure has done for me (twice)! I would be very happy to answer any questions you may have or expand on any part of this testimony if it would help.

Kind regards,

[redacted]

E-mail from [redacted]: FW: Knee operation

[redacted]

Fr [redacted]
Se
To
Cc: [redacted]
Subject: Knee operation

Dear Sirs
I have suffered with long term knee problems since the age of 25, but by the age of 36 my knee completely ruled my life with constant pain, locking, swelling and making my life a complete misery, then I went to see [redacted] who suggested an ACI, which I had in October 2007, which initially worked until 2012, then I had another ACI which has again worked, now the benefit of the last operation is that I now have non of the above complaints, and now the impact it has made in my life, work, social and sport, has massively improved.
I can now do things which I was unable to do in 2007.
Regards

[redacted]

E-mail from [redacted]: ACI cartilage transplants

[redacted]

1 attachment

Private and Confidential

Dear Sirs

I have been asked by [redacted] to contact you regarding a procedure I require which I have been trying to get authorised by BUPA and the NHS since 2013.

About Me

[redacted]

Sex – Male
Marital Status – Married with three children

I am a Partner of a building company based in [redacted] employing fifty member of staff working for Insurance companies dealing with subsidence, fire and flood claims.

I am a voluntary Directo[redacted] Indoor Bowls Club based in C[redacted]nd a member of Surrey County Indoor Bowls Association and the English Indoor Bowls Association.

I am a keen sports man and have played bowls since the age of ten. I have played at a high level representing Club/County and Country. I have won and been in a number of National finals and represented England in the British Isle Championships.

I was also awarde[redacted] the year.

Unfortunately due to the pain and restricted mobility I have been unable to play bowls for the past three years.

History

2003 I was referred by my GP and under BUPA cover to see [redacted] regarding a problem and pains I had with my right knee. A procedur[redacted]hich immediately failed.

2005 BUPA referred me to [redacted]s to carry out a procedure including a micro fracture to my knee. This aga[redacted]
I was then referred under BUPA cover and the recommendation of [redacted] arranged for an MRI scan and sub[redacted]

approved a diagnostic procedure. It was identified that I had damage to my retro patellar surface and MACI/ACI procedure would be required.
This procedure was approved by BUPA and carried out at the Royal National Orthopedic Hospital, Stanmore. The procedure was very successful and I was able to return to a normal life including playing bowls and getting to further National finals.

2013 I started getting pain in my knee so I re-visited [redacted] clinic for assessment. An MRI was authorised and approved by BUPA. It was found that I had further damage and would require an additional MACI/ACI procedure.

2014 I contacted BUPA following diagnosis from [redacted] but I was informed that they no longer cover this procedure. After making a number of appeals to them they would not authorise the procedure.
BUPA suggested they refer me to another Consultant ([redacted], Sports Medicine Sports Medicine Specialist) for a second opinion and to seek an alternative treatment. After being referred I was advised that no other alternative treatments would benefit me other than a MACI/ACI. However this has not altered BUPA's decision not to approve.
[redacted] advised me that he carries out the MACI/ACI under the NHS at the Royal National Orthopedic Hospital, Stanmore as they perform this procedure under the NHS at the hospital.
I was advised to contact my GP, [redacted] to be referred.
Unfortunately after a number of requests for additional information from my GP and [redacted] Clinical Commissioning Group at [redacted] have advised that I am ineligible for consideration.

I wrote to my local Member of Parliament in 2014 for assistance due to the problems I was having obtaining funding from our regional NHS Trust, but he was also unable to gain approval.

Currently my quality of life, both family and work is suffering due to restricted mobility and locking of the knee which affects my daily routine and sleep. I am hoping you will be able to provide me with guidance and your influential assistance to allow me approval for the procedure MACI/ACI required.

I have attached a medical report produced by [redacted] in 2014 which I hope will also assist you.

Could you please acknowledge receipt of this email.

Regards

[redacted]

[redacted]

[redacted].uk

Dear sirs , I had ACI 6 1/4 yrs ago . The result being 6 more years of hard physical activity . And still going strong . The treatment improved my life immensely . Including resolving my depression issues. I would urge you to thing again about financing AC[redacted]as improved my life immeasurably. Yours sincerely [redacted]

E-mail from [redacted]: Autologous Chondrocyte Implantation (ACI)

[redacted]

To: [redacted]repair.co.uk
2 attachments

To whom it may concern,

My name is [redacted] and I was extremely lucky to have been accepted onto the Cartilage Repair trial with Professor James Richardson at the Robert Jones & Agnes Hunt Orthopaedic Hospital.

I have recently been advised that the treatment I had (growing my own cells in the procedure of Autologous Chondrocyte Implantation (ACI)) is no longer going to be supported. I can only speak about my own circumstances, but the transformation to my life thanks to this treatment is truly unbelievable.

I really can't over play what the treatment has meant to me, my wife and children. Before the surgery I was having to take Tramadol pain killers every day, undergo regular pain management sessions and physio & psychological therapy, all paid for by my local NHS trust.

Before my knee took a turn for the worse, I enjoyed regular sporting activities. Sport was a major part of my life, however just before my first child was born I started to experience the problems with my knee. The pain I was experiencing along with the psychological effects of no longer being able to play the sports I had enjoyed since I was a child was crushing. I was unable to kneel down to play with my baby son, even walking with my wife and son caused problems, as the pain would stop me. My mental state had also become a worry, as I had lost a lot of enthusiasm and was also putting on a lot of weight. If you are able to look at my test scores and evaluations through the trial, you'll see just how bad things were for me at that time.

However, just as I was at my worst, this trial was opened up to me. And whilst I can't say that I'm back 100% to my previous self, this operation truly changed my life for the better. I am no longer taking pain killers just to be able to perform simple functions, I am totally pain free. I'm back playing sports and able to run with my children. I have a much healthier lifestyle thanks to this operation, and will be forever grateful for the wonderful work Professor Richardson has done.

I have no idea how much my treatment cost, but I do know that if it wasn't for this treatment that my local NHS trust would have been spending a lot of their resources on me through pain management, physical and psychological therapy, and who knows what would have happened to my marriage and work life.

I really do hope that a compromise can be reached, so this treatment can continue and that others can benefit as myself and my family have. I am also more than happy to help in any way I can should any further questions, tests etc need to be made. I offer all of my test results in a hope that the positive influence of this medical treatment can continue.

Best regards,

[redacted]

E-mail from [redacted]: Autologous Chondrocyte Implantation (ACI)

[redacted]

To: [redacted]

Dear Sir/Madam [redacted]

My name is [redacted] and i am currently a patient taking part in the Active Trial being run at RJAH Hospital in Gobowen Oswestry.

It is my understanding that you are currently reviewing the value of this type of surgery.
The procedure that i have had is a Autologous Chondrocyte Implantation or ACI to my right knee which i had in November 2007.

Before i had the ACI procedure i found myself in a position of pain and discomfort with my knee having to put up with pain,swelling,catching and impaired movement of the knee on a daily basis. I found myself to be taking regular pain medication and putting ice on my knee after work and stopped being as active as i had been.

I stopped playing football for my local team,running and mountain biking in order to protect my knee from being painful and swelling and found that day to day activities also had an impact on my knee.

I had visited my GP on a number of occasions and he made the decision for me to see a orthopaedic consultant at my local hospital, after a outpatient appointment and MRI scan i underwent a arthroscopey which showed that i had damage to the articular cartilage surface on my knee had that he had tried to repair and clean the damaged area, this however turned out to be unsuccessful and the symptoms i had been suffering quickly returned.
During the consultation that followed that procedure i was told that there was nothing more that could be offered to me in the way of treatment at my local hospital and was informed of the trial that had been started at the RJAH hospital and would i be prepared to visit the hospital to see if they could help.

After a consultation at the hospital i accepted the offer of a place on the trial and was randomised to have the ACI procedure with no options left for me locally i was very relieved and grateful that there was a treatment available to me.
It is now just over 8 years since i had my procedure and although it was a long and sometimes painful recovery i am still happy to have had it done and would recommend it to others if they found themselves in a similar position as myself.
I feel that my quality of life has been maintained in terms of being able to continue to work and be able to keep active in a variety of ways.

I understand that you will be comparing this type of procedure against other existing treatments and cost may be a key factor in this, but please consider the fact that i have had both and having been treated with the existing treatments without success i was fortunate to be offered something else, are you going to take that opportunity away from people in my situation going forward, with time and further results and research it could improve and become more of a success in helping to improve the quality of life in others.

I am sure you will take everything into consideration when reviewing the value of having this procedure as an option to offer people suffering with cartilage defects.

Thank you.

[redacted]

E-mail from [redacted] Auotlogous Chondorocyte Implantation (ACI)

26/1/2016 00:16
connor [redacted]
To nice@cartilagerepair.co.uk Copy [redacted]
2 attachments

- 20160125_215939.mp4 (10 MB)
- 20160125_215939.mp4

Dear National Institute for Health and Care Excellence,

In February 2007, Professor Richardson of the Robert Jones and Agnes Hunt Orthopaedic Hospital, Oswestry carried out the ACI procedure on my right knee. Previously, I had very actively played sports including hurling and football. However in 2003 at the age of 41 my sports playing days ended owing to serious cartilage problems in my right knee.

My knee would swell following any form of exercise. The pain was severe to excruciating when weight was applied to the bent knee. I was told by my surgeon at the time that I would require a knee replacement within 15 years.

Since I had the ACI procedure my knee does not now swell following exercise and all pain has subsided. I am fully able to engage again in the sports of hurling and football without any adverse effects.

As a result of this surgery I am able to participate to a much greater degree in sport and therefore maintain a reasonable level of fitness.

FYI I have attached 2 video clips of me playing hurling in recent years. The over 40s hurling video is of a hurling game I played in during the Summer of 2009 which was just 2½ years following the ACI procedure. E.g. I can be seen in action scoring a couple of goals on 35.46mins& 36.36mins (am wearing a yellow bib, a black togs & black helmet). The other video shows me in hurling action in the ball alley in 2015 with a couple of mates. FYI, I am wearing the black and amber coloured jersey.

Yours sincerely.....

[redacted]

E-mail from [redacted]: ACI

[redacted]

To: NICE@cartilagerepair.co.uk

Dear Sir/Madam

I had the 2 stage ACI operation around 6 years ago, before the operation I could hardly put my foot to the floor & was in unbelievable pain, after the procedure & the physio I was able to walk without crutches, & returned to work after several years, I understand the procedure is costly but gave me quality of life, it is worth every penny, please do not scrap it!

Kind regards

[redacted]

Sent from Yahoo Mail on Android

E-mail from [redacted]: ACI

[redacted]

To: [redacted]@cartilagerepair.co.uk

Dear sir, madam

With response your email please see details below.

In 2003 I had the cartilage removed re grown and put back.
Before I had the procedure I was in constant agony, limping while walking which was only small distances due to the pain and discomfort and due to this I was unable to work so therefore I was on incapacity benefit for some time.
Since having the operation I can walk without limping, no more pain, can walk were ever I need to go and whenever required. I also have a job as a cleaner which involves bending and kneeling and without having the procedure I would not be able to do any of these things.
My quality of life had been improved dramatically some things people take for granted with there knees make a big difference to your day to day life when in constant pain and discomfort and once this has been relieved the difference is amazing.

Kind regards

[redacted]

E-mail from [redacted]:

[redacted]CI treatment

[redacted]

Good afternoon,
I would like to provide a brief statement in support of the continuation of MACI treatment by NICE.

I am a 47 year old married mother of two teenagers.
I had suffered acute pain for a number of years, especially when carrying out any weight bearing activity. This included simple activities such as walking and dancing, and also driving a manual car. I was unable to take part in even simple exercise and could not kneel or crouch.
I had undergone months of physiotherapy, an arthroscopy to assess the condition of the knee and steroid injections to try and provide short term relief for the pain. I was told that a knee replacement operation would be inevitable but that I was too young and this would not be considered until I was past 60 years old.
In March 2013, at age 44, I underwent MACI treatment on my left knee.
The benefits brought by the operation are as follows:

- No longer acute pain when carrying out weight bearing activity
- Able to take part in light exercise – dancing, swimming, walking

Overall a much improved quality of life.

I feel that to reject the continuation of this treatment for people in a similar position such as myself would be a travesty – it was my only viable treatment and without it, my quality of life in my 40's and 50's would be dramatically reduced.

Kind regards,

[redacted]

[redacted]

E-mail from [redacted]

[redacted]

To NICE@cartilagerepair.co.uk Copy James Prof. Richardson and 2 others

To whom this may concern-

Thank you for the opportunity to express my opinion on this treatment.

The start of my adventure/treatment was sometime in 1994 (please feel free to check my records). After a slip at work, a shard of bone broke away inside my knee. After numerous operations, (cleaning loose cartilage, pinning bone, cleaning cartilage, removing bone, cleaning cartilage) and years of wearing knee supports it's now 2007 and the outlook was bleak. I was informed that there were no more options left for me, and with no cartilage left, and with the on-set of arthritis, it would leave me inactive within 5 years. At 39 I was devastated. I was informed of a medical trial that was taking place at R.J.A.H and that I fitted the criteria. I met with the team - headed up by Prof. Richardson and signed up. I had the A.C.I operation in August 2008. The operation and it's outcome is 85-90% of what I expected. The rehab and time off work were 50% longer I expected, but well worth it.

As I have repeatedly answered on the 12 month evaluation questionnaires - I would recommend this operation to others .

THANK YOU !!

Please feel free to contact me direct - [redacted] if you require any further information.

Regards,

[redacted]

E-mail from [redacted]: MACI

[redacted]

Re; NICE,gid-tag 446 review of Autologous Chondrocyte Implantation, for painful articular cartilage lesion

Following a history of knee problems and various procedures to try and alleviate the problem (debridement, meniscus trim etc) I was still having great difficult with day to day activities. My life revolved around chronic knee pain and the limitations that this put upon me. For example I had great difficulty driving, working and walking due to the pain and coping with the medications I was on. I lost confidence in myself, had a limited social life and struggled to keep positive.

Within a short time I was offered a MACI within a trial, it seemed a wonderful opportunity so I was really keen to be involved.

The operation and recovery went well. I could now look to the future and set myself activities to do so I could get back to a normal life as quickly as possible. My knee steadily improved, I was able to exercise, swim, drive a car, work, go on holidays and go for walks, basic things that we take for granted but which have a devastating effect on you when you are not able to do them. The MACI was a brilliant option for me and my knee!

[redacted]

E-mail from [redacted]: ACI cartilage repair

[redacted]

I wish to express my thanks and also my disappointment that the ACI treatment that I received in 2009 may possible being discontinued due to funding.

I had a number of years and issues with my one knee where cartilage broke off when it liked, causing me issues with my knee giving way, swelling, unable to walk long distances and being unable to do what I wanted to do social and fitness wise. After my 4 op, I was recommended to Prof Richardson's clinic in 2009 for assessment and then 2 ops to perform ACI.

Although, not gone fully back to sporting life, I can not emphasis more how this op changed my life from struggling as mentioned above from to 7 years -touch wood- of pain free normal active life.

Without this operation, I don't think this would of been possible and I am grateful to Prof Richardson and his team for this. I'm am 100% sure that there are others down the line that would benefit, like I did, from this type of operation and feel that curtailing the funding of this would only be to the detrimental of others.

I would fully support further development of cell therapies and hope this e mail goes towards rethinking and retaining the necessary funds to continue this very successful practice.

[redacted]

Patient under Prof Richardson @ Robert Jones & Angus Hunt Hospital from 2009 to current - with 3 years remaining in the trial.

Sent from my iPad

Support for NICE review of Cartilage repair surgery

E-mail from [redacted]: Support for NICE [redacted]ry

[redacted]

I'd like to give my support to the ChondroSelect Cartilage repair treatment on my knee which has changed my life in a way which I couldn't have envisaged.

For the last 7 years my left knee has been slowly deteriorating and the pain has gradually been getting worst and restricting my quality of life. I loved playing sport including football , squash and cross country running but had to slowly give this up because the pain was getting too much, long distance walking was also starting to become a real problem along with playing actively with the kids.

I've had a number of operations to treat the knee which have only gone so far as to patch up the problem not solve it .

The ChondroSelect Cartilage repair treatment I received last year has given me real peace of mind that I can live with no more knee pain for a good length of time to come . After 6mths since surgery I'm able to swim , cycle , walk and play with my children without the same restrictive pain I used to get. I'm also less conscious about the injury now that things are starting to settle down and this is a massive weight off my mind !

I support the case for this treatment being continued to help other patients like myself benefit from such advancing technology.

Your sincerely

[redacted]

E-mail from [redacted] · Funding concerns

[redacted]

Dear Sir

I am writing to express my grave concerns and disappointment at the recent news that ACI may no longer be funded in the future.

I underwent ACI in 2006 following an injury to my knee in 1996. I suffered 10 years of intermittent swelling, pain and inactivity which was not successfully treated by 2 microfracture operations. My job as a physiotherapist was under threat and I feared a lifetime of disability and suffering.

When I entered the clinical trials at Oswestry in 2006, I had very low expectations and goals of merely being able to walk effectively, continue to work and support my young family.

A year or two following surgery I was beginning to regain some confidence in my knee and found that I could work it hard without it swelling or becoming painful. I began to work harder and found I was able to return to playing badminton at club level, (something I had ruled out prior to ACI). I have clocked up 30 years working for the NHS as a physiotherapist and now as an arthroplasty practitioner and I have no mobility restrictions.

This week I will be celebrating my 50th birthday and I shall be spending it by representing my county playing badminton for one of our veteran teams. This is a far higher level than I achieved pre-injury and something I would have had no chance of doing following injury.

I cannot put a price on the quality of life that was afforded me by having ACI surgery. The operation has kept me out of surgery for ten years and has kept me working continuously for our NHS. The health economics involved require no higher intelligence thinking. I fear this would have been a very different case had I not been fortunate enough to enter that clinical trail as I would not have been able to fund the operation privately.

I hope you are able to reconsider your stance with regards to funding so that other patients are afforded the same chance to live a fuller life.

Yours sincerely

[redacted]

E-mail from [redacted]: Support For Knee Cartlidge Repair Surgery

[redacted]

[redacted]repair.co.uk

Dear Sir / Madam,

I am writing this email to show my support for Cartlidge Repair Surgery. I fisrt suffered damage to my knee cartlidge over 17 years ago from playing in a charity football match where a tackle went wrong and from then I had undergone several keyhole procedures to repair and maintane the damage caused to my cartlidge but I constantly suffered with on-going pain and discomfort with my knee. I would often find my self struggling to climb stairs or stand for any period of time in an outside environment as it would cause such pain I felt like crying. I underwent a MACI procedure on 18.03.11. The procedure helped relieve a lot of my pain and discomfort with my knee, I have been informed that within time I may require a knee replacement procedure but the MACI has without doubt postponed me needing this for many many years to come, and allowed me very valuable time to create many memories with my young daughters to join them in leisure activities such as bike riding, swimming and walking as I before avoided these activities as not to cause undue pain in my knee. I know have no discomfort since the procedure and only occasional pain within my knee aslong as I follow the instructions and advice from my surgeon (Tim Spalding). I feel that this type of surgery would benefit many people that would otherwise be left with no option as to either suffer with the pain and discomfort for many years or end up having to have a knee replacemnent very early in life and before it would normally be recommended.

Kind Regards

[redacted]

E-mail from [redacted] ACI stem cell [redacted]ation-[redacted]

[redacted]
To nice@cartilagerepair.co.uk
To whom it may concern,

I have been asked to contact you as a patient who has undergone an ACI stem cell transplantation by Professor Tim Briggs.

I was a 52 year old active woman with what turned out to be a 2cm hole in my left femoral cartilage which was very painful and severely impacting on my daily life. I had been a very sporty person with running and swimming as my main means of exercise which I was no longer able to do.

I was very fortunate to be referred to Prof Briggs who thought that the ACI transplant was pretty much the only option left to me other than a partial knee replacement (which I didn't want) to relieve my pain.

Thankfully he went ahead with the transplant and it has been a tremendous success.

6 years on I am back to being able to participate in all the sports I enjoy. I have swapped running for cycling as although I could still run if I wanted to I didn't think it was wise or fair to Prof Briggs hard work to subject my knee to such impact when I have many other sports and activities that I can still enjoy.

I would strongly recommend this surgery to anybody who is in a similar situation to the one that I was in and remain eternally grateful to Prof Briggs.

I hope this information has been useful to help in your decision making.

Kind regards

[redacted]

E-mail from [redacted]. ACI surgery

[redacted]

To whom it may concern,

I would just like to write in support of the continuation of ACI intervention for condral defects of the patella. I underwent this surgery on both of my knees with a realignment. Prior to this my right knee was the first to become impaired. I was restricted to a limp, terrible pain sitting down and driving. Previously, I had been very active, sporty and fairly fit. This was a real shock to me and very debilitating I experienced some very dark days, where I wandered how I would actually manage to function. I am a social worker in adoption and was struggling to maintain a good working week.

When I heard of the above surgery it gave me hope, where there was none. I had my right knee done, it was amazing. Professor Richardson was very clear with me about what the surgery entailed and what I would have to do to rehabilitate. Then my left knee was found to have a similar defect, I had the same surgery on my left knee.

I have never looked back, this has given me my life back, I can run, Cycle and swim. I am not in pain sitting down, using the stairs and driving. Every day tasks are not a problem any more. My mental health is good, as I am able to engage in the sports I love and I am completing triathlons. I am working and have only lost time out of work for the surgery and immediate recovery. I am paying my taxes and not claiming benefits which could have been my fate.

In the long term this procedure will be very cost effective, as I am no longer requesting assistance form the health service as I am fine.

Thank you for your attention,

[redacted]

Sent from my iPad

E-mail from [redacted]: [redacted]
comments ACI funding support letter

[redacted]

This email has no content
DOCUMENT

Please find enclosed my letter of support for continued ACI funding.
I have had ACI to the right knee with Patello with Semoral realignment in January 2015. I am female aged 63 and enrolled on the ascot trial. Before my knee operation I was bawling against constant knee pain, knee swelling and knee locking. With joint instability. Constantly worries about my knee giving way or even dislocating.
The benefits of the operation and my expected out come is to be independently functional in every day activity with improved mobility, reduced pain (apart from healing pains) decreased swelling and no instability. My profession is ongoing and each month I feel as though I have reached another level of improvement.
The impact that this has made on my life: progress is steady and I am very pleased that I have had the opportunity to have this procedure using the latest technology for Cartlidge Repair. Had I had not this procedure I feel as though my knees would have deteriorated even further, as I get older, seriously effecting my mobility and wellbeing. I am able to resume life activities and start to be independent.
Kind regards

[redacted]

E-mail from [redacted]: ACI operation on my right Knee

[redacted]

It is now approaching 8 years since i had this operation and i feel as though i must let you know of my experience with this proceedure.

My history was as a semi-professional rugby player up until i had an incident on the rugby field.

At first i had a routine arthroscopy and where it was clear that i had a serious issue with the cartilage on my knee. So eventually I was told about this "new trial" at the Robert James Agnes Hunt hospital and was then introduced to to Prof. Richardson.

After several meetings and scans i was selected to take part in the trial.
I had ACI on my RIGHT knee

After my initial arthroscopy and subsequent micro-fracture my right knee felt weak and was prone to give even whilst attempting to cross the road.
As you can imagine this didn't make me feel safe and secure.
At the time i had an office based job as a civil servant and my partner had just opened a shop and i was supposed to join her and work in the shop however this had to
be cancelled as i wouldn't be able to be on my feet for most of the day. so i had to remain in the civil service.
I was also unable to undertake any real exercise and as a now ex rugby player where fitness and training was a way of life i became overweight and i felt "down". i was now in that viscious circle and my self esteem and my general well being was spiralling down.

After i had undergone the proocedure and was having physiotherapy on my knee i stared to feel confident and better about myself. I had hoped at least to be able to cross over the road safely.

6 - 9 months after the operation I was able to take the dogs on long walks and had also started to exercise and build up the strength in my knee.

I feel that if I really do not know what my life would be like if I hadn't have had this operation I am now working full time with my partner in the shop and we have now moved into a much larger shop for approaching 6 years and day day duties that before the operation I had to rely on other I do now without even having to think about
it.

Since the operation I have even played rugby on a few occasions and now exercise on a regular basis. I have completed a few 10 km runs, Cycled coast to coast

several times and completed the Manchester to Blackpool bike ride for charity. I have also completed several 100 mile bike rides. I have even learnt how to swim properly and has a result of this I completed my first "sprint" triathlon in 2012. Since then I have done a few more "sprint" triathlons and in 2013 and 2015 i completed a "middle distance" triathlon (1900m open water swim 56 mile bike ride followed by a 13.1 mile run) and this year I will be doing a full marathon in April in Manchester

I really do have to thank the Prof and his team and this operation for what I feel gave me my life back and I certainly would have no hesitation in recommending this operation.

[redacted]ed to discuss then I can be contacted on this e mail or my mobile is [redacted]

Yours thankfully

[redacted]

E-mail from [redacted]: Comment on MACI [redacted] Briggs

To whom it may concern.

I have now had 2 MACI procedures to my right knee after suffering from the knee locking, giving way and generally causing pain which made me walk with a limp. I had previously undergone an initial micro drilling procedure upon the same knee but after initial improvement this had failed within 6 months. The first MACI procedure was to repair the cartilage on the medial condyle in 2010, this was a grade 4 damage, the operation went well as did the recovery and overall the change in the knee was great. At the end of my rehabilitation I was able to return to the gym to exercise and the ability to walk around without pain, locking and giving way of the knee.

The 2nd Maci procedure was completed in 2012 and was to repair cartilage damage behind the patella of the right knee, this again was grade 4 damage for which I exhibited similar symptoms to the original injury. This again impacted on my ability to exercise and walk around without pain and also impacted my ability to drive for my work. Again after rehabilitation the pain within the knee was removed and I have been able to return to gym and now walk without a permanent limp although after my latest check-up and MRI damage has been observed to other areas of the cartilage in the right knee that is now causing some discomfort, this damage is not associated with the 2 areas where the MACI procedures have been completed.

Overall I'm very happy with the success of the 2 procedures and I believe that they have allowed me to keep exercising as well as allowing for a good and active quality of life which I believe would not have been the case without them as being in my late 30's / early 40's at the time of the operations was deemed to be too young to receive knee replacement surgery.

If you have any questions or comments regarding the above then please do not hesitate to contact me,

Regards,

[redacted]

ACI Procedure [redacted]

E-mail from [redacted]: ACI Procedure

[redacted]

[redacted]uk

To whom [redacted]

My name is [redacted] on 21/02/2012 i had my 2nd stage .cartilage repair done by the MACI technique.

Prior to this operation in 2010 i had a microfracture procedure on my right knee which was not successful and my doctor Mr Crane advised me of this procedure Mr Spalding was doing and referred me to him in March 2011 to see if i would be suitable for me to undergo.

After meeting Mr Spalding and discussing the procedure i decided it would be worth trying as i was only 43 and a knee replacement was out of the question as i was too young and at this point my mobility was very poor and was in a lot of pain when bending or putting any pressure through my knee.

I was amazed how quickly i recovered from the operation and i even walked out of the hospital without crutches although i was in a brace. The pain was minimal and after a few weeks physio i was able to return to work

I can honestly say this operation changed my life i have lost a lot of weight due to me being able to do fitness and go on long walks and generally do everything i used to do before my knee problems.

I know this procedure has a high cost but for me it was worth it because without this procedure i would probably not be able to walk unaided now

I cant thank Mr Spalding and is team enough for given me the chance to have this procedure and give me my life back.

I really hope that this procedure is allowed to continue so other people can experience the life changing surgery i did, it really does work, four years on and i still do not have any issues at all with my knee.

Your Sincerely

[redacted]

feedback on cart[redacted]

E-mail from [redacted]: feedback on cartilage repair

[redacted]20:16

[redacted]

To NICE@cartilagerepair.co.uk

I understand you are looking at clinical feedback regarding cartilage repair while evaluating the operations availability for the future.

I was an early recipient of this treatment as a young man in my 40s with severe osteoarthritis of my knee.

At the time I could not walk more than quarter to half a mile without very severe pain and having to stop.

The operation has enabled me to have a full active life. I was back playing golf, surfing, active with the children and able to go on long hikes in this country and abroad. I have still retained my own knee joint 15 years on and would hope to maintain it for several more years before a knee replacement may be required.

The operation has made a major impact on my quality of life. Had the alternative , a total knee replacement been carried out then the quality of life may not have been so good and I would almost certainly have need of revision in the near future and possibly another in my lifetime. I would recommend someone else with my symptoms to strongly consider this option for treatment.

I hope this information is of help in your evaluation.

Yours sincerely

[redacted]

E-mail from [redacted]: ACI

18/2/2016 08:50

To NICE@cartilagerepair.co.uk

To whom it may concern

I am writing in support of the ongoing use of ACI for articular cartilage degeneration.

To give a potted history I underwent total lateral menisectomy in both knees in 1986 and 1987 when I was just 16 years old. Over the next 20 years as you can imagine as a young and active person I went on to develop significant OA changes GR3/4 in my lateral compartments which reduced my ability to function. I was not able to kneel or squat, had constant pain and in the end was limited to walking less than a mile before paying the consequences for a week. Sleep was disturbed and there was significant swelling in my knees following a routine day at work from just being on my feet. My left knee was more affected than my right knee with areas of Gr4 changes compared to areas of Gr3/4 in the right knee. I found it very difficult to complete a days work as a musculoskeletal out-patient physiotherapist due to the requirements to frequently change position to be able to treat my patients.

I underwent surgery at the age of 39 and had a ACI performed in my left knee and had microfracture in my right knee 9 months later. I am therefore possibly in a small minority group of people who can obviously compare the 2 techniques in term of outcome and the effect that this has had on my symptoms.

Both knees have significantly improved in terms of no longer having ongoing persistent pain. I am now able to kneel and squat if required. I can walk freely in terms of distance with minimal consequence and can cycle and use the cross trainer, however when I get symptoms it is always in my right knee. This was the knee that was less symptomatic pre surgery and was the knee that I had the microfracture in. The knee with the ACI is not symptomatic and I am now 5-6 years from surgery without signs of any deterioration towards my pre-operative state.

I have been able to return to some clinical work as a physiotherapist (although I am mostly in operational management nowadays) and in my time as a therapist also have seen others who have significantly benefitted from ACI. They too have been able to return to sport / fitness activity which has meant that they are no longer a burden on the NHS for ongoing care of their symptoms.

I would therefore recommend the continuation of this surgery for specifically selected patients who otherwise would continue to be a burden on the NHS. Without it these patients face more major surgery at a younger age with the potential limitations that this brings and the increased likelihood for further revision replacement later in life at a greater cost to both the patient physically and psychologically and to the NHS as system in the future.

[redacted]

ACI

E-mail from [redacted]: ACI

[redacted]

To NICE@cartilagerepair.co.uk

I write to you to provide my experience of Autologous Chondrocyte Implantation which I had performed on my left knee approximately 4 years ago.

I had long standing issues with my left knee which were causing me constant pain and discomfort. I experienced swelling, weakness and often my knee would give way particularly when walking, exercising, using steps and kerbs.

As a full-time care home manager and father of two I relied heavily on being able to mobilise, run, walk and enjoy time with my family. Due to the pain and discomfort I wasn't able to do these things.

I had undergone previous procedures on my knee which were successful to a point. The ACI procedure which was offered to me at my local hospital has made the biggest difference with longer lasting improvement. The procedure has lead me to improve my physical activity with sport and exercise and the physical fun time I have with my family. I used to worry and be anxious when walking, cycling etc. as I knew my knee would give way and swell up.

I appreciate the ACI procedure is complex and was a big deal when it came to recovery, however the benefits far out way this. This procedure has literally changed my abilities to work and enjoy activities with my children. It's a procedure which must continue to be offered as it surely reduces long term use of other facilities and services and improves the lives of those who receive it.

Regards

[redacted]

Sent from my iPad

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ABSTRACT

- ACTIVE is a prospective randomised trial comparing cell grafting techniques for the repair of articular cartilage in the knee (autologous chondrocyte implantation (ACI) or matrix-induced ACI (MACI)) with standard treatments for patients who have had a failed primary treatment for chondral or osteochondral defect(s) in the knee.

- The target recruitment is at least 480 patients over 5 years. Thirty centres (28 in the UK, 2 in Norway) have so far agreed to participate.

- Patients will be randomised to:
  1. ACI (surgeon can choose either ACI or MACI or a sub-randomisation between two types of matrix-assisted ACI: MACI and Chondron) or
  2. Standard treatment

- Investigators choosing traditional ACI have the option of further randomising patients to have a patch made of (a) periosteum or (b) collagen membrane.

- The choice of cell grafting technique and standard treatment will be pre-specified by the recruiting surgeon, individually for each patient.

- Patients in the Standard treatment arm may have debridement, abrasion, drilling, microfracture, mosaicplasty, or AMIC according to clinical indication.

- The primary outcome measure will be time to cessation of benefit of treatment.

- Secondary outcomes will be functional knee scores (Lysholm, Cincinnati, IKDC) and Quality of Life measures (EQ5D) at intervals up to 10 years post operation.

- Health economic analysis is an integral part of the study.

1. BACKGROUND TO TRIAL

1.1. Chondral lesions

Articular cartilage provides a smooth, low-friction surface in the knee joint and dissipates the compressive and shear forces generated by movement under load. High, supra-physiological loading can fracture the joint through the cartilage or through the sub-chondral bone, giving rise to chondral or osteochondral defects, respectively. Such injuries are most commonly sustained as a result of sporting injury or trauma. In the condition osteochondritis dissecans (OCD), loss of a fragment of cartilage or bone and cartilage appears to occur spontaneously without trauma.

Patients who experience symptoms after cartilage injury complain of knee pain, knee swelling, joint locking, and instability. The inability to work and play sport severely diminishes the quality of life of these patients. The long-term sequelae are not well documented although 55% of OCD patients who sustained joint damage as young adults went on to develop severe osteoarthritis earlier than patients with idiopathic OA (1). This is an important point, for although arthroplasty is an excellent procedure in the elderly (>60 years), the failure rate in younger patients is much higher - 20% failure in the first 10 years, 49% within 20 years (2). Effective early treatment of these defects would reduce disability and may prevent early onset osteoarthritis secondary to these conditions, so eliminating or postponing the need for joint replacement and reducing the likelihood of revision arthroplasty.

Currently there is no uniform approach or gold standard for the management of hyaline cartilage defects in the knee. Good results following simple debridement were reported in 60% of cases at 5 years (3). Replacement of the cartilage with synthetic materials (e.g. carbon fibre) does not provide a permanent solution. In other surgical procedures, termed marrow stimulation techniques (drilling, abrasion, microfracture), the base of the debrided defect is breached to cause bleeding of the bone and clot formation in the defect. The clot becomes populated with bone marrow stromal cells from the intra-trabecular space of the subchondral bone that produce a fibrocartilaginous matrix. As this does not have the hyaline structure of normal cartilage, there is some question as to how long this can withstand the stresses of joint movement, however good outcomes up to 7 years after surgery have been reported (4). Transfer of osteochondral grafts from minor load bearing parts of the joint into the defect (mosaicplasty) has also been shown to be effective for smaller defects up to 4cm^2; (5) but this procedure is not recommended for larger lesions.

1.2. Autologous chondrocyte implantation

In recent years, autologous chondrocyte implantation (ACI) has been used increasingly for the treatment of chondral and osteochondral defects (6). In this procedure, a small sample of cartilage is removed from a minor load bearing part of a patient's damaged joint; chondrocytes are isolated from this and grown in monolayer culture in vitro. When the cell number has been amplified sufficiently (3-5 weeks to generate 8-12 million cells), cells are implanted into the debrided defect in a second planned operation. The cell suspension is retained by a membrane, which may be either periosteum or a collagen membrane, sutured to the edges of the defect and sealed with fibrin. This procedure has the potential to generate repair tissue that is well integrated with the surrounding cartilage and offers a durable surface. With up to eleven-year follow up of patients who have had this procedure, good to excellent outcome has been reported in approximately 80% of patients, depending on the anatomical location of the defect (7). Importantly,

histological analysis of the repair tissue after ACI shows features characteristic of hyaline articular cartilage (7, 8, 9, 10).

Many surgeons and patients have great expectations of ACI. More than 12,000 people have now received ACI world-wide. **However, as yet, the long term benefit of ACI over other treatments has not been conclusively demonstrated**. The study with the longest follow up (7) shows continuing benefits from ACI after eleven years, but with no comparator group. However, two recent small-scale short term studies have reported that microfracture (11) or mosaicplasty (12) give results as good as or better results than ACI. A third study reported the outcome of ACI to be better than mosaicplasty (13).

The original ACI procedure made use of the patient's own periosteum to cover the defect and retain the implanted cells. More recently decreased morbidity has been reported using a membrane made from porcine collagen membrane (8, 13). A further development of the ACI procedure is to seed the cells onto the collagen membrane in the laboratory, and at the second stage the seeded membrane is attached over the defect using fibrin sealant. This technique known as matrix-induced ACI (MACI®) (provided by Genzyme) can be performed via a mini-arthrotomy, thus saving operating time and offering a less invasive alternative to ACI. One-year follow-up results of a study by the Stanmore Group (14) suggest ACI and MACI® provide a similar clinical outcome.

A further matrix version of ACI is Chondron™ provided by Sewon Cellontech. With Chondron™ the cells are suspended in a gel which acts as a scaffold for holding the cells within the defect, thus avoiding the need for a patch or sutures. Chondron has been applied to more than 1500 patients in.

Previously the ACTIVE trial was designed to include only ACI. However, following Main Research Ethics Committee (MREC) approval in March 2007 the use of MACI® or ACI (according to surgeon preference) is allowed in the ACI arm of the trial and following MREC approval in March 2008 Chondron™ is an allowable option. If used, Chondron will be sub-randomised against MACI® within the ACI arm of the trial. In this document all references to the ACI treatment arm should be interpreted as meaning ACI or MACI/Chondron.

In December 2000, the National Institute for Clinical Excellence (NICE) published guidance on the use of Autologous Cartilage Transplantation for full thickness cartilage defects in knee joints (Technology Appraisal Guidance no 16). The guidance recommended an adequately powered, randomised trial comparing ACI against the best alternative treatment for patients who have had a previous simple debridement that has not relieved symptoms. A further recommendation was that robust cost effectiveness studies should also be carried out. This guidance was updated in 2005 making it clear that every patient treated with ACI should be enrolled in a clinical study designed to generate robust and relevant outcome data.

In 2003, The Medical Research Council agreed to fund, and the Department of Health agreed to support the present trial called ACTIVE - **A**utologous **C**hondrocyte **T**ransplantation / **I**mplantation **V**ersus **E**xisting standard treatments.

1.3. Aims of the trial

The ACTIVE trial aims to find out if there is a clinical benefit of ACI compared with any of a range of non-cell grafting techniques that the surgeon considers is the best alternative. This flexibility allows the wide range of individual factors in a

patient with a chondral defect of the knee, which has already failed previous treatment, to be taken into account. Surgeons can choose the type of surgery with which they are most accustomed or which they personally consider to give best results. In order to avoid potential biases and so that trial analyses can be stratified by the type of control intervention that would have been received, the intended control procedure will be asked at randomisation.

Surgeons may opt to further randomise ACI patients in order to compare the patient's own periosteum with collagen membrane for retaining the cells.

Surgeons recruiting patients to this study must have an open mind and be undecided whether any of the trial treatments is a clear benefit over one of the alternatives for the particular patient. Patients must be appropriate for ACI or one of the alternatives. As ACI involves 2 procedures and both ACI and mosaicplasty involve significant surgery, patients should have symptoms that warrant such treatment.

Originally patients with osteochondral defects (OCDs) defined as bone loss exceeding 3mm depth, were excluded from the trial. However, in recent years bone grafting techniques have developed to the point where the bone can be successfully restored and a cartilage regenerative treatment can be attempted as part of the same procedure. Therefore, as of March 2008 this protocol includes OCDs provided the surgeon carries out a bone grafting technique aimed at restoring the bone to within 3mm of the surrounding bone. Patients with a chondral defect exposing bone on the tibia are excluded. Patients where osteotomy of the femur or tibia or meniscal transplant is planned will also be excluded. These patients are better studied separately.

The randomisation process will take into account factors that might affect outcome and, to avoid the possibility of bias, the outcome will be assessed by an independent observer who has no knowledge of the treatment allocation, through structured questionnaires and functional assessments.

Previous studies of ACI have focused on an improvement in functional knee score. In ACTIVE the principal outcome will be the survival of any benefit. The definition of failure will be the point at which the patient's symptoms or activity level have not improved, or are worse. The first time point for measuring cessation of benefit will be 12 months post-treatment. A detailed health economics analysis will take into account the cost of different treatments allocated.

2. TRIAL DESIGN

The main question being addressed by ACTIVE is:

- does ACI offer a better clinical outcome at 3, 5 and 10 years post-operation than alternative procedures for the repair of isolated chondral defect(s) of the knee that remain symptomatic following previous treatment?

The question will be addressed by direct comparisons between patients allocated ACI and patients allocated a pre-specified control intervention not involving ACI.

The target is to recruit at least 480 patients in up to 30 centres (28 in the UK and 2 in Norway) over 5 years.

2.1. Large, simple trial: minimal extra investigations and data collection

To make large-scale recruitment feasible, the ACTIVE trial is "streamlined" so as to impose as little extra workload on clinicians as possible, beyond that required to

treat their patients. The single test used for assessing eligibility for the study is one which would be used in standard practice for patients due to receive ACI, and the important prognostic information will be collected at randomisation. Many of the scales used are patient rated, and cessation of treatment benefit will be assessed by a blinded assessor provided by the study.

2.2. Randomised comparison of ACI versus a preferred control option: eligibility based on uncertainty

There is no general consensus as to which patients are likely to derive the most benefit (if any) from ACI. In addition, the patients who may be eligible for ACI therapy are a heterogeneous group, and the therapy which they would receive in the absence of ACI may vary. Not all procedures are suitable for all types or sizes of chondral defect, and there may be understandable reluctance to randomise patients to receive a treatment that has already failed. For this reason, ACTIVE adopts a flexible pragmatic design in order to assess the relative efficacy of ACI in a clinically wide population of patients.

In ACTIVE, therefore, eligibility is based not on rigid entry criteria but on the **"uncertainty principle"**. That is, if the doctor or the patient considers, for any reason, that there is a **definite** indication for, or a **definite** contraindication against ACI then the patient is not eligible for ACTIVE. If, on the other hand, both doctor and patient are **substantially uncertain** whether or not to use ACI then that patient is **eligible to be randomised between ACI and another procedure (if the patient also meets the criteria listed in Section 3.1**.) In these circumstances, randomisation is both scientifically and ethically preferable to the uninformative alternative of not randomising and treating the patient in an *ad hoc* way outside of a study. Eligibility based on uncertainty has been used in several previous trials e.g. the "ISIS" trials, the MRC International Stroke Trial, and the MRC QUASAR trial (QUASAR Collaborative Group) (15) and has been shown to simplify trial procedures and to facilitate large-scale recruitment of an appropriately heterogeneous group of patients. The decision on whether the indication is **uncertain**, and the criteria on which it is based, are left entirely to the responsible physician. Even within one participating hospital different doctors may decide differently as to the categories of patient for whom the indication for ACI is uncertain.

3. TRIAL RANDOMISATION

3.1. Simple eligibility: symptomatic chondral defect, failed previous procedure, no "definite" indications for, or "definite" contraindications against ACI

To encourage widespread recruitment, the eligibility criteria are made deliberately pragmatic. A patient is eligible for the trial if:

- the patient is not participating in any other clinical trial involving the knee, either currently or in the last 6 months
- there is a symptomatic chondral defect on the medial or lateral femoral condyle or trochlea, or patella needing surgery. Patients with 2 defects in the same compartment may be included if the defects are to be treated in the same way.
- the defect is considered suitable for ACI and at least one of the existing alternative treatments
- there has already been a previous procedure (which may be arthroscopic washout or ACI) carried out on the same defect at least 6 months previously which has failed to relieve symptoms

- there is substantial uncertainty as to whether to treat with ACI or with conventional therapy
- the patient is shown to be negative for serology tests required by the cell provider. This includes HIV, hepatitis B and C, syphilis, and may also include human T cell lymphotrophic virus (HTLV) I and II.
- For any eligible non-English speaking patients translation services will be employed as and when necessary.

Not all defects are necessarily associated with a likelihood of worthwhile benefit and the following list includes conditions where ACI would not be considered helpful in treating a knee defect. There are also some contraindications to ACI therapy. Thus, a patient is ineligible for the study if subject to any of the following:

- a defect of greater than 12 cm^2 in total area
- total meniscectomy, or untreated malalignment of the patella
- osteoarthritis, inflammatory condition, history of mesenchymal tumours
- known anaphylaxis to any product used in chondrocyte preparation
- low probability of compliance with physiotherapy or follow-up, including a major life-threatening condition.

3.2. Central randomisation:

Randomisation will be performed centrally by the University of Birmingham Clinical Trials Unit (BCTU) and patients can be entered either by telephone (Freephone 0800 953 0274 within UK, +44 (0) 121 687 2319 elsewhere), Fax (+44 (0) 121 687 2313) or over the internet (https://www.trials.bham.ac.uk/active). The Local Co-ordinator will need to provide all necessary details about the patient and reference to the Patient Entry Form (Appendix 1) beforehand may be helpful in preparing for randomisation.

To ensure balance between patient groups, treatment allocation will be by minimisation, with stratification variables:

- intended control treatment option
- size of chondral defect
- age
- pre-operative functional knee score
- femoral or trochlea/patella defect.

Randomisation will not be stratified *a priori* by centre, as this can lead to unacceptably high rates of prediction of future treatment allocations, thereby introducing potential selection bias (16). Instead, centre effects will be investigated by *post hoc* stratification of analyses.

In order to reduce the possibility of bias that may be introduced because of different waiting times for different operations, randomisation should take place as close as possible to the intended time of operation. It is recognised however, that certain centres may have difficulty in managing their caseloads with the uncertainty of whether a patient will be requiring ACI or a potentially shorter operation. In order, therefore, to ensure that resources are not under-utilised, there will be the option of a pairwise randomisation(17). Clinicians may choose to randomise two patients simultaneously, in the knowledge that one patient will receive ACI and the other will not. This procedure is currently in use with good results in the MRC-funded PD-SURG trial.

4.SURGICAL TECHNIQUES

4.1.Debridement

An essential feature of debridement is removal of all “unstable” cartilage from the edge and base of the defect which is then washed away. In a randomised trial comparing arthroscopic washout with debridement for isolated medial femoral condylar lesions, good results for debridement were reported (3).

4.2. Abrasion/drilling

In addition to removing loose fragments as in debridement, the base of the defect is debrided until small bleeding points are seen. This bleeding is best confirmed with the tourniquet down.

4.3. Microfracture

This technique was introduced 20 years ago and is a modification of the drilling technique. Advantages of microfracture over drilling are that no over-heating or burning of the subchondral bone is created. The first step is accurate debridement of all unstable and damaged cartilage in the lesion including the calcified layer down to the subchondral bone plate. All loose or marginally attached cartilage from the surrounding rim of the defect is also debrided to form a stable perpendicular edge of healthy cartilage. An arthroscopic awl is then used to make multiple holes in the defect, 3-4 mm apart, but not so close that they could break into each other, as the subchondral bone plate should be kept intact. It is also easier with a curved awl compared to a drill to penetrate the defect perpendicular to the surface during an arthroscopic procedure.

Following microfracture the defect is filled with a so- called “super clot”. This is the key to the entire procedure and this clot is believed to be the optimal environment for the body’s own pluripotential marrow cells to differentiate into stable tissue within the lesion. Acceptable clinical results up to 5 year and then a decline have been reported for most marrow-stimulating techniques for cartilage repair (18). However, Steadman (4) recently published outcomes of microfracture for traumatic chondral defects in which 7 years after surgery, 80% of the patients rated themselves as improved.

4.4 Autologous Matrix Induced Chondrogenesis (AMIC®)

AMIC® has recently been marketed as a new technique that aims to improve on microfracture by using Chondro-Gide® membrane to hold the “super clot” in place, providing a matrix for new cartilage tissue formation (19, 20). The membrane is attached with fibrin glue or sutures via an arthrotomy.

4.5. Mosaicplasty

The technique of Mosaicplasty or Osteochondral Cylinder Transplantation (OCT) was first described by Matsusue et al (21) in 1993. In the technique, osteochondral plugs are taken with a cylindrical cutting device and used to fill the cartilage defect. Plugs are usually taken from the peripheries of both femoral condyles at the level of the patellofemoral joint and replaced as a "mosaic" to fill the defect. The technique is usually done as an open procedure in all but the smallest defect as care has to be taken that the harvest site matches the donor site for its contour and thickness of cartilage. Plugs should be tightly fitting so that they do not later loosen. Healing of the donor site is usually good.

The main advantage of this technique is that treated defects are filled with mature hyaline cartilage straight away. The disadvantage is donor site morbidity, which

limits the size of defect that can be readily repaired to 1-4cm^2. In larger defects where multiple plugs are used, there may be lack of congruity between the edges of the plugs and gaps between plugs may allow synovial fluid to escape and cause cyst formation.

The largest single series to date is that of Hangody (5) who described good to excellent results after 10 years in 92% of patients undergoing mosaicplasty of the femoral condyle.

4.6. Autologous Chondrocyte Implantation (ACI)

The technique of Autologous Chondrocyte Implantation was first described by Brittberg et al in 1994 (4). In ACI, culture-expanded autologous chondrocyte cells are injected into a chondral defect underneath a patch of periosteum. A number of studies, including long-term follow up in the Swedish study, have been encouraging with reports of over 80% of patients having excellent or good results at 5-11 years after ACI (6).

In ACI stage 1 (arthroscopic) a harvest of articular cartilage is taken and sent to the laboratory for cell preparation. The protocol of the cell supplier must be followed carefully. It is essential that sufficient cartilage is harvested to allow the chondrocyte culture to be established. All the cultivated cells are used for the implantation and therefore no cells are stored for any other purpose. While most surgeons take the cartilage harvest from the upper medial femoral condyle, recent research (21) suggests that cell yield is comparable from harvests taken from the lateral ridge, trochlea or intercondylar notch. Different instruments (ronger, rasp, curette, gouge) may be suited to different sites.

In ACI stage 2, which is usually carried out as an open procedure 3-4 weeks later, the edge of the defect is debrided until stable cartilage is obtained. Care is needed at the leading edge of a defect as there can be detachment of cartilage from subchondral bone that is not readily apparent. The base of the defect is debrided with care to avoid bleeding. Internal osteophytes can either be excised with a sharp osteotome or impacted with a punch. Bleeding from bone can be inhibited by an adrenalin solution.

To harvest periosteum an oblique incision is made in the line of the intrapatellar nerves below the joint line. This exposes the anteromedial tibia just below the pes anserinus. A template (e.g. suture pack foil) of the size of the defect is generally used and applied to the periosteum and an incision is made 2mm outside the edge of the endplate with a fresh 15 blade. This is then raised with a fine periosteal elevator. The periosteum is cleared of all fat and transferred without delay to the chondral defect, with the cambium layer facing in towards the defect. The periosteum must not be allowed to dry out. Collagen membrane should be used only after training and according to the manufacturer's instructions. Sutures placed in opposite corners initially helps to keep the membrane/periosteum central. Interrupted sutures, 3mm apart, are most generally used. In the case of large defects extending to the edge of a condyle it may be necessary to use a 'K' wire and drill holes through bone to hold sutures. Fibrin glue is applied to the edge of the defect and the patch then tested for `water-tightness'. When satisfactory, the volume of cells recommended by the supplier is then inserted under the patch and the wound is closed.

For matrix-induced ACI and Chondron stage 1 is carried out as described above for ACI. Once at the laboratory the cells for MACI are grown onto collagen

membrane for 3-4 weeks. Stage 2 is performed via a mini-arthrotomy in which a template of the defect is made and used to cut the seeded membrane to size. Fibrin sealant is applied to the subchondral bone plate and the MACI® membrane is sealed into position using gentle pressure. With Chondron the cells are expanded then mixed with a tissue fibrin sealant and this mixture is injected over the defect.

4.7. Post operative rehabilitation

Appropriate post-operative rehabilitation is essential whichever treatment is allocated. Recommended protocols for each of the treatment options will be made available.

As the aim of debridement is symptomatic relief rather than tissue regeneration, there is no need for protected weight-bearing, hence post operative rehabilitation is with crutches and full weight-bearing as able to ensure return to full function.

Following abrasion, drilling, microfracture, AMIC or mosaicplasty, immediate post operative continuous passive motion (CPM) and restricted weight bearing to protect regenerating tissue is recommended for all patients. After ACI, MACI or Chondron 6 hours post–operative rest allows for cell adherence. This is followed by CPM for 3 days and restricted weight bearing with crutches for up to 8 weeks. An exercise bike is a good way for all patients to continue with CPM. The idea is for them to spin against low resistance for an hour a day or more.

5. REGULATIONS AND TRAINING

5.1. Cells

The autologous chondrocyte preparations used in this trial must be produced in accordance with the Code of Practice for Tissue Banks published by the Department of Health (February 2002) or under an accredited GMP scheme for human somatic cell therapies.

The Medicines and Healthcare products Regulatory Agency (MHRA) has advised that chondrocytes are not regarded as a medicine under current legislation, thus it is not currently a requirement to register the ACTIVE trial under the European Clinical Trials Directive (2001/20/EC).

5.2. Collagen membrane

The collagen membrane used to seal the chondral defect in ACI must have CE Mark certification for that purpose. It is not a requirement to register trials of CE marked products with the Medical Devices Agency.

5.3 Training requirements

Surgeons

All recruiting surgeons will be experienced in performing knee surgery and will be required to confirm that they have previous experience of each of the techniques they may use. As the trial is a randomised design, patients may be allocated to either the ACI arm or to the alternative treatments arm. Surgeons must therefore have previous experience of ACI (with periosteum and with collagen membrane). In the alternative arm, the surgeon will select the appropriate treatment option. This must be an option with which the surgeon has had previous experience.

To participate in the ACTIVE trial the minimum experience for each procedure before recruitment to the trial is regarded as one of the following

- At least 1 procedure supervised by an already experienced surgeon
- 5 unsupervised procedures

If necessary, surgeons can gain experience of ACI under the supervision of the Chief Investigator, Professor Richardson. In addition, for ACI, each surgeon must have had training in the use of a collagen membrane. This training can be provided by Geistlich and is a requirement for all surgeons using the Geistlich membrane. Geistlich will provide special workshops for surgeons participating in the ACTIVE trial. Training in the MACI® technique will be organised by Genzyme Biosurgery. Training in Chondron™ will be organised at the RNOH, Stanmore.

The Department of Health Interventional Procedures Programme (November 2003) requires that any surgeon undertaking a new procedure for the first time must seek approval from the local Clinical Governance Committee. As surgeons participating in ACTIVE will have used all the procedures before, this will not be necessary. Approval would not be necessary in any event when a procedure is used within a protocol approved by the REC.

Local study coordinators
Each site's Principal Investigator should identify a local coordinator to take responsibility for obtaining patient consent, organising blood tests, randomisation of patients and scheduling the allocated procedure. They will continue to work with the trial manager throughout the trial. Training days for local coordinators will be arranged before recruitment starts at each site.

Independent assessors
Each site should identify a suitable person (e.g. a physiotherapist) who will be trained centrally in outcome assessment. To remain blinded this person should not be involved in the usual clinical care of the patient. Since this person will need to obtain the pre-operative functional knee scores and quality of life indicators, this training will also take place prior to recruitment.

6. OUTCOME MEASURES

6.1. Data collection

Functional knee scores, Quality of Life indicators and resource usage data, will be collected pre-operatively, then at 2-3 months, 6 months, 1, 3, 5,and 10 years in clinic (by interview and self assessed) and annually in intervening years by patient using post or electronic means (see Schema, p. 18). To maintain contact with patients over the 10 year follow-up and to avoid sending questionnaires to deceased patients the Trial Manager/local study coordinators will use the National Strategic Tracing System to trace patients who may have moved to a new address, and to identify any patients who have died.

6.2. Primary: Cessation of benefit of treatment

A cessation of benefit form (Appendix 2) will be completed by a trained, blinded, independent assessor. Patients will be advised that treatment allocation must not be revealed and that both legs should be covered.

Cessation of benefit forms will normally be completed at the pre-specified follow-up points. In addition, if the patient is due to receive a further procedure on the previously treated knee, the trial office should be contacted, and a cessation of benefit form filled out to determine knee status prior to further procedure.

Using the cessation of benefit form the assessor will confirm:

- the current independently assessed Lysholm form is complete
- the patient self-assessed Lysholm knee questionnaire is complete
- whether the patient's knee has improved or not since pre-op in terms of swelling, range of motion and pain.

The form will then be returned to the Trial Office.

The 3 criteria to be used for assessment of no benefit or cessation of benefit are:

- No gain in independently assessed Lysholm knee score compared with pre-operative score
- No gain in patient's self–assessed Lysholm knee score compared with pre-operative Lysholm score
- Overall knee status judged by the assessor as not improved from pre-operative condition.

Cessation of benefit is defined as 2 out of the 3 criteria being met and will be identified by the Trial Office.

6.3. Secondary: Functional knee score

A knee specific measure, the Lysholm (Appendix 3 & 4) assessed both by blinded observer and by patients and the patient-assessed IKDC (Appendix 5) and Cincinnati Sports Activity rating (Appendix 6) will be used.

The Lysholm Knee Score (23) is an eight-item questionnaire of knee function. Scoring is on a 100-point scale with 25 points for pain, 25 points for stability, 15 points for locking, 10 points each for swelling and stair climbing and 5 points each for limping, squatting and support. The Lysholm score has been validated and is widely used (24). However, the scale was originally designed to assess patients following knee ligament surgery with a special emphasis on symptoms of giving way, and this is reflected in the weighted scoring system.

The IKDC form incorporates a demographic form, current health assessment form, subjective knee evaluation form, knee history form, surgical documentation form, and knee examination form. The IKDC subjective knee evaluation form will be used in the ACTIVE study. This score was designed to detect changes in patients with a variety of knee conditions including articular cartilage lesions as well as meniscal and ligament injuries. It has been validated as a knee-specific score for patients with a wide variety of knee problems (25). It is divided into three parts relating to symptoms, function, and sports activity. Scoring responses from the questionnaire are transformed to a scale with range 0-100 points using a standard formula according to item-response theory.

The Cincinnati knee rating system was first published in 1983 (26, 27). In all it has 11 components, including a subjective clinician's rating, patient's perception, symptom rating, Sports Activity Scale, Activities of Daily Living Function scales, Sports Function scales, Occupational rating scale, overall rating scheme, physical examination, laxity of the knee on instrumented testing and radiographic evidence of degenerative joint disease. Again, the Cincinnati system is in wide usage and has been validated in two studies (1, 24). For the purposes of ACTIVE, the Sports Activity Scale, Activities of Daily Living Function scales and Sports Function scales will be used.

There is quite an overlap between these forms. This is because these questionnaires have been used in other studies with which comparison will be made. Each of the forms needs to be completed IN FULL at each scheduled time.

6.4 Quality of life indicator-EQ5D

Knee injuries can have a significant impact on a patient's physical function and quality of life and this may be reflected in a general health score. General health measures also assess psychological health components and make comparisons that can be used for health economic analysis. The cost-benefit evaluation of ACI is increasingly important. EQ5D (28) (Appendix 7) is a general health assessment tool that gives a rating based on five questions and a health status based on a visual analogue scale. This form is very simple and quick to administer and is in wide usage. No licence is required for non-commercial research.

6.5. Resource Usage

Use of health service resources and privately incurred costs will be recorded at all the intervals (see schedule and schema) using a structured Resource Usage questionnaire (Appendix 8). This will enable health economic evaluation (see 9.1)

7. STATISTICAL ANALYSIS

7.1 Sample Size and Power Considerations

The sample size for this trial has been estimated based on data that suggest that approximately 40% of patients treated with conventional therapies require an additional surgical intervention within 5 years (3). Since patients requiring a further procedure are almost certain to have suffered a cessation of benefit as defined in Section 6, event rates in this trial are likely to be slightly higher. The original proposed sample size of 660 would enable the detection of a proportional reduction of 30% (40% to 28%) in the failure rate with 90% power at p=0.05 (29). A smaller sample size of 480 would provide 80% power to detect the same 30% reduction in numbers requiring an additional procedure. Should event rates be higher, then the proportional reduction that can be detected will be correspondingly smaller (e.g. 50% to 37.5%, a proportional reduction of one quarter). The proposed reduction is equivalent to an improvement in median time to failure of around 2 years, representing a cost per failure-free year of approximately £8,000. The minimum sample size of 480 patients would also provide 90% power to detect a small to moderate effect size of 0.3 of a standard deviation in the continuous outcome variables (e.g. Lysholm knee score) at p=0.05.

7.2 Data Analysis

The same methods of analysis will be used for the main ACI versus standard treatment, and for the sub-randomisation between types of membrane and types of matrix-assisted ACI. The primary endpoint is time to the cessation of treatment benefit as defined in Section 6. Data for this endpoint will come from the prespecified assessment time-points, as well as the additional assessments undertaken when a patient presents for a further procedure. Analysis of this endpoint will be by means of standard log-rank methods and stratified analyses presented using odds ratio plots (30). If, during the first year following surgery, the patient would have been deemed to have derived no benefit from surgery at all assessment points (using this endpoint) then the procedure is deemed to have failed, and the patient will be analysed as suffering an event on day 1. For the continuous outcome measures, repeated measures analyses will be performed on the change from the baseline scores, using standard multilevel mixed modelling techniques using SAS PROC MIXED. Such analyses have the

advantages of being able to combine results from different time-points to maximise power, and also to investigate the precise form of any benefit (whether, for example, any treatment benefit, should one exist, increases or decreases with time). Multilevel modelling also allows for suitably stratified analyses to be performed.

Subgroup analyses are limited by statistical power and can produce spurious results particularly if many are undertaken. For this reason, the only prespecified subgroup analyses are those defined by the stratification variables (intended control and cell-grafting treatment options, size of chondral defect, age, pre-operative functional knee score, femoral or trochlea/patella defect), as well as period of study, to investigate any potential learning effects. In addition, to investigate possible differences in the effectiveness of ACI between centres, analyses stratified by centre will be performed.

7.3 Data Monitoring & Ethics Committee

During the recruitment period interim analyses of major endpoints and safety data will be supplied annually (or more frequently if requested) in strict confidence, to an independent Data Monitoring and Ethics Committee (DMEC) along with updates on results of other related studies and any other analyses that the committee may request. The DMEC will advise the chair of the ACTIVE Trial Steering Committee (TSC) if, in their view, the randomised comparison in ACTIVE has provided both:

- "proof beyond reasonable doubt"[1] that for all, or for some, types of patient ACTIVE is definitely indicated or definitely contraindicated in terms of a net difference in time to cessation of benefit
- evidence that might reasonably be expected to influence the patient management of many clinicians who are already aware of the other main trial results.

Unless this happens, however, the Steering Committee, the collaborators and all of the central Trial staff (except the statisticians who supply the confidential analyses) will remain ignorant of the interim results.

8. SAFETY

ACI is a well-tolerated procedure, and side-effects of treatment are expected to be rare, but collaborators should notify the trial office immediately of any serious unexpected adverse experiences believed to be due to any of the trial treatments by telephoning the study office and subsequently by completion of the Serious Adverse Events Form (Appendix 9).

The DMEC will consider data from interim analyses, and any additional safety issues for the trial and will recommend to the TSC if the trial should be stopped for any safety reasons.

9. HEALTH ECONOMICS

Collection and analysis of data relating to economic evaluation will be supervised by Professor Marilyn James at the Centre for Public, Health Liverpool John Moores University.

[1] Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but a difference of at least three standard deviations ($p \approx 0.002$) in an interim analysis of a major endpoint may be needed to justify halting, or modifying, the trial prematurely. If this criterion were to be adopted, it would have the practical advantage that the exact number of interim analyses would be of little importance, so no fixed schedule is proposed.

9.1. Costs
Health economic evaluation will be from a societal perspective with both public sector and private cost data collected. Private costs will include days off work as well as any privately financed health care related to the knee. Health service costs will include any adverse events and treatments due to knee damage. As the trial will be multi-centred, unit costs specific to each centre will be collected for the major cost items including type of ACI (which may vary with supplier). Unit costs will also be collected for alternative conventional treatments, and main other knee related treatments that patients may require over the period of the trial.

9.2.Cost effectiveness analysis
Health economic analysis will use EQ5D (28) to estimate cost per Quality Adjusted Life Year (QALY). Cost effectiveness will be assessed both in terms of cost per QALY and per year free of further surgery. In addition ICERs (incremental cost effectiveness ratios) will be determined from usual care to ACI or MACI. Cost Effectiveness Acceptability Curves will be plotted for each of the options.

9.3. Modelling
Modelling will be required to combine trial and non-trial data, and for sensitivity analysis exploring the implications of a range of assumptions on the results. In addition, modelling will explore issues of patient drop out and censoring of data.

10. ORGANISATION
The **Host Institution** for the ACTIVE trial is Keele University. The Medical Research Council (MRC) is the funder and Keele University is the Sponsor. Keele University is accountable to the MRC for the conduct of the research and adherence to the principles of the Research Governance Framework.

The **Chief Investigator** is Professor James Richardson. **Co-investigators** are Professor Richard Gray, Professor Marilyn James and Professor George Bentley.

The Chief Investigator has nominated a **Trial Steering Committee** (TSC) and a **Data Monitoring and Ethics Committee** (DMEC) and these have been approved by the MRC (see inside cover).

10.1. Ethical approval
The ACTIVE protocol has been approved by the TSC and also by the Multicentre Research Ethics Committee (MREC). Before recruitment at any site can begin, the Local Research Ethics (LREC) Committee must give `Locality' approval and local R&D management approval must be obtained.

10.2. Trial Manager
The Trial Manager is Dr Heather Smith (full time during the recruitment phase, then decreasing) who will set up and coordinate collaborating sites, support patient recruitment, be responsible for budget management, and for the collection and reporting of outcome data.

10.3. Local organisation
Each collaborating site will formally identify a local **Principal Investigator** who will take responsibility for local conduct of the study in compliance with the Research Governance Framework and for obtaining LREC and local R&D management approval.

Keele University will put in place an agreement with each of the Collaborating sites setting out the requirements and responsibilities.

As soon as LREC and local R&D management approval have been confirmed, and an agreement is in place, the Trial Manager will visit the site to provide staff training and the ACTIVE trial materials. Randomisation can then begin.

Because of the many possible treatment allocations in this trial, the task of identifying eligible patients and fully informing the patient prior to obtaining consent should be with the recruiting surgeon, supported by the local co-ordinator.

10.4. Local study co-ordinators

Financial support will be provided to each collaborating site for assistance with recruitment. This will be pro-rata dependent on patient numbers and will be part of the collaborative agreement which the University of Keele will make with each recruiting centre. Collaborating sites are advised to identify appropriate personnel as local study coordinators. This person will obtain and document consent, organise blood tests, randomise patients and subsequently schedule the allocated procedure.

10.5. Randomisation

Potential eligible patients will normally be identified by the surgeon at the out-patients clinic where interested patients will receive a Patient Information Leaflet (Appendix 10). At this stage the surgeon will complete Parts A&B of the Patient Entry Form (Appendix 1) and pass this form on to the study coordinator. At the next out-patient appointment or at a separate visit the study coordinator will see the patient to ensure he/she is fully informed about the trial. If the patient agrees to participate in the trial he/she will sign a consent form (Appendix 11) and the patient's GP will be informed (Appendix 12). The study coordinator will then complete all questions in Part C of the Patient Entry Form (Appendix 1), and submit all details using the online randomisation system or by phoning Birmingham Clinical Trials Unit. The allocated procedure will then be advised, and the treatment scheduled according to local practice. If it is anticipated that there will be a delay in treatment (i.e. more than 6 months), the patient details will be registered and the Trial Office will then contact the local co-ordinator nearer the time of surgery. If the patient remains eligible for the study, and surgery is anticipated within three months, randomisation will then occur and the allocated procedure advised. Delaying randomisation will minimise pre-treatment drop-out after randomisation which would dilute the power of the study. When treatment has been completed the Treatment Record Form (Appendix 13) will be completed by the surgeon and entered onto the database by the co-ordinator.

10.6. Independent (blinded) outcome assessors

In order to minimise the potential for bias, a pre-operative assessment and some of the outcomes will be assessed by a `blinded' assessor who has no knowledge of the treatment allocation and must not be told by the patient, study co-ordinator or surgeon. The patient's leg will be covered with tubigrip. The assessor should have no part in the normal care of the patient. The schedule of blinded assessments is displayed on page 18. Assessments are mainly in the form of questionnaires (functional knee scores, Quality of Life measures and resource usage) and functional assessments although a simple examination to detect swelling of the knee will be required. It is envisaged that the assessment could be carried out by a physiotherapist and a `per-event' payment will be available. Training will be

provided centrally early in the study. On-going support will be available from the Trial Manager.

10.7. Research costs

The Medical Research Council funds the research costs of the study only. Research costs include the trial manager, central statistics and health economics evaluation, collecting self-assessed outcome data from patients by post, training for local study coordinators and independent assessors and the costs of the TSC and DMEC. It also provides some support for the input of time of local study coordinators and for the independent outcome assessors, depending on recruitment. This will be part of the individual agreements between Keele University and each collaborating site.

10.8. Treatment costs

The costs of the treatments in any trial fall within normal contracting arrangements. Because autologous chondrocyte implantation (ACI) is more expensive than the standard treatments, the Department of Health is supporting the *excess treatment* costs through a Central Subvention fund. Parallel arrangements are in place for Scottish and Welsh patients through the Wales office of R&D and Scottish Executive Health. Each recruiting centre has been advised on how to access the Central Subvention fund in a letter from the Head of the NHS R&D Policy, Department of Health, October 2003.

10.9. Service Support costs

There are additional costs consequent to the trial that fall into this category. These are the additional time required in an outpatient clinic to inform and recruit patients, the costs of pre-randomisation blood tests for those patients who would not normally need tests and 4 outpatient appointments over 10 years for each patient, additional to normal practice. The level of the service support costs has been agreed by the Department of Health. In line with the Concordat that exists between the Medical Research Council and the NHS, organisations are expected to meet these costs from their NHS R&D Budget. Organisations not in receipt of NHS R&D funding, or for whom the service support costs present difficulty should contact the Department of Health for advice about the *ad hoc* arrangements. From 2008 this funding can be claimed through the UKCRN (portfolio ref. 2432).

10.10. Indemnity

There are no special arrangements for compensation for non-negligent harm suffered by patients as a result of participation in the study. ACTIVE is not an industry-sponsored trial and so ABPI guidelines on indemnity do not apply. Normal NHS indemnity liability arrangements for clinician-initiated research will apply in ACTIVE.

Geistlich Pharma has offered to supply Chondro-Gide® collagen membrane free of charge for recruited patients under a Material Transfer Agreement. Chondro-Gide® is a CE marked non-active implant, normally available for use in ACI. Geistlich Pharma has not been involved in the design or conduct of the trial in any way and will have no special access to data.

10.11. Publication

The ACTIVE trial is a long-term study with 10 year follow up. Given the scale of the project it is envisaged that a number of publications will be generated. The first principal analyses to be reported in peer-reviewed journals will be undertaken in year 5, or after 3 years follow-up.

The success of ACTIVE depends entirely on full collaboration of a large number of people. Depending on the publication policy of the journal(s) any publication will either be in the name of the study i.e. ACTIVE with all collaborating leads identified or with an authorship including all those who have collaborated in the study.

It is essential that the trial protocol is followed and that no additional investigations conflict with either the treatments or the outcome measures. For this reason it is requested that any proposals for additional studies related to the trial be referred to the Trial Steering Committee for consideration. Any intention to publish a case report or case series from an individual site must first be advised to the Trial manager for approval by the Trial Steering Committee and this will be part of the agreement between each collaborating site and the Host Institution.

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SCHEDULE OF ASSESSMENTS

	1 Pre-op Clinic	2 2/3 months Clinic	3 6 months Clinic	4 1 year Clinic	5 2 year by post	6 3 years Clinic	7 4 years by post	8 5 years Clinic	9 6 years by post	10 7 years by post	11 8 years by post	12 9 years by post	13 10 years Clinic
Blinded Observer Lysholm	X	X	X	X		X		X					X
Blinded Observer Cessation of benefit				X		X		X					X
Patient Lysholm	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient IKDC	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient EQ5D	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient Cincinnati	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient Resource usage	X	X	X	X	X	X	X	X	X	X	X	X	X

TRIAL SCHEMA

Eligibility

- Symptomatic chondral/osteochondral defect(s) on the medial or lateral femoral condyle or trochlea suitable for either ACI or one of the existing conventional treatments (debridement, abrasion, drilling, microfracture, AMIC, mosaicplasty)
- Not more than 2 defects, not kissing and total area not greater than 12 cm^2
- Surgical treatment/washout for the same defect, carried out at least 6 months previously, that has failed
- No concurrent total meniscectomy/osteotomy or untreated malalignment of patella
- No generalised osteoarthritis, inflammatory condition or history of mesenchymal tumours
- Likely to comply with appropriate physiotherapy
- HIV, Hepatitis B & C, Syphilis, HTLV I & II negative (or tests as required by the cell supplier)
- Patient not in clinical trial involving the knee, currently or in last 6 months

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Randomisation

- Obtain patient's written informed consent
- Serology: all tests as required by cell provider completed and negative
- Specify ACI or MACI options (which may include a sub-randomisation as listed below)
- Decide treatment in the event patient is randomised to `alternative' arm of trial
- Ring randomisation service and answer all questions on Registration Form
- Eligible patients will be randomised

Randomise

ACI or MACI (according to choice)

- With periosteum or
- With collagen membrane or
- sub-randomised to periosteum vs. collagen

- MACI or
- Sub-randomised to MACI vs. Chondron

ALTERNATIVE (debridement, abrasion, drilling, microfracture, mosaicplasty, AMIC)

Pre-operative Assessment

(i) Independent observer
Semi-structured interview
Physical/functional assessment
Lysholm knee score

(ii) Patient Self-assessment
Lysholm knee score
Cincinnati score
EQ5D
IKDC

Treatment

When the above assessment has been completed and confirmed, the ACTIVE treatment allocation will be issued. Treatment will be completed as soon as possible

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Follow up

(i) Clinic assessments at 2/3 & 6 months & 1, 3, 5 & 10 years post-op

(i) Independent (blinded) observer	***(ii) Patient self-assessment***
Semi-structured interview	Lysholm knee score
Physical/functional assessment	Cincinnati score
Lysholm knee score	EQ5D
IKDC	IKDC
Cessation of benefit	Resource usage

(ii) Patient self-assessment postal questionnaires at 2, 4, 6, 7, 8, & 9 years post-op

Lysholm knee score
Cincinnati score
EQ5D
IKDC
Resource usage

ACTIVE PATIENT ENTRY FORM

APPENDIX 1

You will need to answer the questions on this form when randomising, either by phone on 0800 953 0274 (+44 (0) 121 687 2319 outside UK), or web randomisation on https://www.trials.bham.ac.uk/active

When patients are identified prior to randomisation, surgeon should complete parts A & B and pass form to local trial coordinator. At randomisation, local trial coordinator should check that parts A & B are complete and correct before randomising the patient.

PART A: IDENTIFYING DETAILS

Or attach hospital sticker here if ALL details given

Hospital Name ..... Responsible clinician .....

Patient's Surname ..... Given Name(s) .....

Patients' Address .....

Date of Birth (dd:mon: yyyy) ..... : ..... : ..... Sex: M ☐ F ☐ Tel. No. .....

Hospital number ..... N.H.S. Number .....

PART B: PATIENT'S MEDICAL DETAILS

Affected Knee Left ☐ Right ☐ Both (ineligible) ☒

Date of most recent procedure (dd:mon: yyyy) ..... : ..... : ..... Type: .....
(n.b. randomisation must be at least 6 months post procedure)

Type of defect: Medial femoral ☐ Trochlea ☐ Lateral femoral ☐ patella ☐ Predicted size ..... cm^2

PRE-RANDOMISATION ELIGIBILITY CHECKLIST If OCD, predicted depth of bone ..... mm

Generalised OA, inflammatory condition or history of mesenchymal tumours? ☐ No ☒ Yes (ineligible)

Untreated malalignment of patella or unstable knee? ☐ No ☒ Yes (ineligible)

Concurrent total menisectomy or osteotomy? ☐ No ☒ Yes (ineligible)

Intended STANDARD treatment: ☐ Debridement ☐ bone graft ☐ Drilling ☐ Microfracture ☐ Mosaicplasty ☐ AMIC

Intended CELL-GRAFTING treatment :

☐ ACI (membrane) ☐ ACI (periosteum) ☐ ACI (rand. periosteum /membrane) ☐ MACI ☐ MACI (rand. Chondron/MACI)

Expected date of surgery (mon:yyyy) ..... : ..... (NB Surgery must take place within 3 months of randomisation)

Please pass this form now to the local trial coordinator who will contact the patient at a later date.
When ready to randomise, coordinator should check parts A and B and complete the rest of the form.

(Pre-registered patients) Details in Parts A&B been checked and/or corrected? ☐ Yes ☒ No (ineligible)

If patient decides not to take part, record below the reasons (if known) and return this form to the trial office

.....

PART C: RANDOMISATION DETAILS

BLOOD TEST RESULTS - if required prior to randomisation – check with cell company Date of test (dd:mon:yyyy) ..... : ..... : .....

HIV ☐ Negative ☒ Positive (ineligible) Hepatitis B ☐ Negative ☒ Positive (ineligible)

Hepatitis C ☐ Negative ☒ Positive (ineligible) Syphilis ☐ Negative ☒ Positive (ineligible)

Has the patient given written informed consent? ☐ Yes ☒ No (ineligible)

Have all pre-randomisation assessments been completed? ☐ Yes ☒ No (ineligible)

PLEASE HAVE THE PATIENT-RATED INDIVIDUAL ITEM LYSHOLM SCORES TO HAND WHEN RANDOMISING

TREATMENT ALLOCATION

ACTIVE Trial number ☐☐☐☐

☐ ACI (periosteum) ☐ ACI (membrane) ☐ MACI ☐ Chondron

☐ Debridement ☐ Bone graft ☐ Drilling ☐ Microfracture ☐ AMIC ☐ Mosaicplasty

Please use the patient's trial number on all correspondence / forms sent to the trial office. Please fax or send a copy of the consent form to the ACTIVE trial office and arrange for baseline assessments to be entered onto the ACTIVE database or sent to the trial office.

Contact Person ..... Telephone .....

N.B. After randomisation, follow-up data will be requested, even if the allocated treatment is not given or the diagnosis is changed.

ACTIVE Trial Office, Robert Jones and Agnes Hunt Orthopaedic Hospital, Oswestry, Shopshire, SY10 7AG. Fax: 01691 404170

ACTIVE

APPENDIX 2

PRIMARY OUTCOME
Cessation of benefit assessment form

FORM IDENTIFICATION 3mt / 6mt / 1yr / 3yr / 5yr / 10yr *(circle as appropriate)*

Extra Assessment: ..... / ..... / ..... *(add date if applicable)*

ACTIVE Trial No. ☐☐☐☐ Patient's Initials …… Patient's DoB ..... / ..... / .....

This form is to be completed by the independent assessor who is blinded to treatment allocation. During the assessment patients are asked not to reveal their treatment allocation and both of their legs should be covered.

Section A

	No	Yes
Has the treatment option been revealed to the assessor?	☐	☐
Has there been an additional injury to the trial knee?	☐	☐

Section B

Is the current independently assessed Lysholm form complete? **Yes** ☐

Is the current patient self-assessed Lysholm form complete? **Yes** ☐

In the assessor's view has the patient's knee improved or not compared to pre-operatively? (e.g. swelling, range of motion, pain, functional performance, impact on quality of life)

Please refer back to your assessment notes then delete one: improved / not improved

Which treatment would you guess this patient had?

ACT ☐ or Alternative ☐ (please specify) .....

Name of assessor .....

Signed ..... (please sign) Date ..... / ..... / .....

Date Completed ..... / ..... / .....

Date Entered ..... / ..... / .....

Please enter this data into the ACTIVE database (if available) and post a copy of the form together with copies of the other forms from this assessment to the ACTIVE Trial Office, ARC, RJAH Orthopaedic Hospital, Oswestry. SY10 7AG. Please ensure that all original forms are securely filed.

LYSHOLM KNEE SCORE-FORM APPENDIX 3

INDEPENDENT ASSESSOR

FORM IDENTIFICATION	Pre-rand / 3mt / 6mt / 1yr / 3yr / 5yr / 10yr *(circle as appropriate)*
	Extra Assessment: ..... / ..... / ..... *(add date if applicable)*
ACTIVE Trial No. ☐☐☐☐	Patient's Initials …… Patient's DoB ..... / ..... / .....

This questionnaire has been designed for the Independent Assessor to complete after interviewing and assessing the patient (but not by reading the questions out to patient). Please complete for the affected knee only.

PAIN

1 ☐ None
2 ☐ Intermittent during severe exertion
3 ☐ Marked, during severe exertion
4 ☐ Marked, on or after walking more than 2km
5 ☐ Marked, on or after walking less than 2km
6 ☐ Constant

INSTABILITY

1 ☐ No giving way
2 ☐ Rarely, during athletics or other severe exertion
3 ☐ Frequently, during athletics or other severe exertion
4 ☐ Occasionally, in daily activities
5 ☐ Often, in daily activities
6 ☐ At every step

LOCKING

1 ☐ No locking and catching sensation
2 ☐ Catching sensation but not a locking sensation
3 ☐ Locking occasionally
4 ☐ Frequently
5 ☐ Locked joint upon examination

SWELLING

1 ☐ None
2 ☐ On severe exertion
3 ☐ On ordinary exertion
4 ☐ Constant

LIMP

1 ☐ None
2 ☐ Slight or periodical limp
3 ☐ Severe and/or constant

PTO

STAIR-CLIMBING

1 □ No problems
2 □ Slightly impaired
3 □ One foot at a time
4 □ Impossible because of knee

SQUATTING

1 □ No problems
2 □ Slightly impaired
3 □ Not beyond 90 ^{0}
4 □ Impossible because of knee

SUPPORT

1 □ None
2 □ Cane or crutch
3 □ Weight-bearing is impossible

Name of assessor .....

Date Completed ..... / ..... / ..……..

Please enter this data into the ACTIVE database (if available) and post a copy of the form together with copies of the other forms from this assessment to the ACTIVE Trial Office, ARC, RJAH Orthopaedic Hospital, Oswestry. SY10 7AG. Please ensure that all original forms are securely filed.

ACTIVE

LYSHOLM KNEE SCORE-FORM APPENDIX 4

PATIENT SELF-ASSESSED

FORM IDENTIFICATION Pre-rand / 3mt / 6mt / 1yr / 2yr / 3yr / 4yr / 5yr / 6yr / 7yr / 8yr / 9yr / 10yr *(circle as appropriate)*

Extra Assessment: ..... / ..... / ..... *(add date if applicable)*

ACTIVE Trial No. ☐☐☐☐ Patient's Initials …… Patient's DoB ..... / ..... / .....

This questionnaire has been designed to give information as to how your knee has affected your ability to manage in everyday life. Please answer every section and tick the box to the left of the statement that applies to you for your affected knee only. If more than one statement applies to you tick the one that most closely describes your situation.

PAIN

1 ☐ I have no pain in my knee
2 ☐ I have intermittent pain in my knee during severe exertion
3 ☐ I have marked pain in my knee during severe exertion
4 ☐ I have marked pain in my knee on or after walking more than 2km
5 ☐ I have marked pain in my knee on or after walking less than 2km
6 ☐ My knee is in constant pain

INSTABILITY

1 ☐ My knee never gives way
2 ☐ My knee rarely gives way during athletics or other severe exertion
3 ☐ My knee frequently gives way during athletics or other severe exertion
4 ☐ My knee occasionally gives way during daily activities
5 ☐ My knee often gives way during daily activities
6 ☐ My knee gives way with every step I take

LOCKING

1 ☐ I experience no locking or catching sensation
2 ☐ I do experience a catching sensation but not a locking sensation
3 ☐ I occasionally have a locking sensation
4 ☐ I frequently have a locking sensation
5 ☐ I have a locked knee now

SWELLING

1 ☐ My knee does not swell
2 ☐ My knee swells on severe exertion
3 ☐ My knee swells on ordinary exertion
4 ☐ My knee is constantly swollen

LIMP

1 ☐ I have no limp
2 ☐ I have a slight limp or periodical limp
3 ☐ I have a severe and constant limp

PTO

STAIR-CLIMBING

1 □ I have no problems climbing stairs because of my knee
2 □ My stair-climbing is slightly impaired because of my knee
3 □ I climb stairs one foot at a time because of my knee
4 □ Stair-climbing is impossible due to my knee

SQUATTING

1 □ I have no problems squatting
2 □ My squatting is slightly impaired because of my knee
3 □ I can't squat beyond 90 ^{0}
4 □ Squatting is impossible because of my knee

SUPPORT

1 □ I am not using any kind of support
2 □ I am using a stick or crutch
3 □ Weight-bearing is impossible for me due to my knee(s)

Has anything gone wrong with your knee (complications)? Please list below

Please answer the following question only after you have had your operation

1 □ I am extremely pleased with the operation – would recommend it

2 □ I am pleased with the operation

3 □ I am no different to before the operation

4 □ I am worse than before the operation

5 □ I am much worse than before the operation – wouldn't recommend it

Thank-you for completing this questionnaire.

Please Insert the date when you completed this form ..... / ..... / ..……..
and return in the pre-paid envelope together with your other forms

For Assessor to complete:

Date Entered ..... / ..... / ..……..

Please enter this data into the ACTIVE database (if available) and post a copy of the form together with copies of the other forms from this assessment to the ACTIVE Trial Office, ARC, RJAH Orthopaedic Hospital, Oswestry. SY10 7AG. Please ensure that all original forms are securely filed.

ACTIVE

IKDC KNEE FORM

APPENDIX 5

FORM IDENTIFICATION Pre-rand / 3mt / 6mt / 1yr / 2yr / 3yr / 4yr / 5yr / 6yr / 7yr / 8yr / 9yr / 10yr *(circle as appropriate)*

ACTIVE Trial No. ☐☐☐☐ Patient's Initials …… Patient's DoB ..... / ..... / ……..

SYMPTOMS*:

*Grade symptoms at the highest activity level at which you think you could function without significant symptoms, even if you are not actually performing activities at this level.

1. What is the highest level of activity that you can perform without significant knee pain?

1 ☐ Very strenuous activities like jumping or pivoting as in basketball or soccer
2 ☐ Strenuous activities like heavy physical work, skiing or tennis
3 ☐ Moderate activities like moderate physical work, running or jogging
4 ☐ Light activities like walking, housework or yard work
5 ☐ Unable to perform any of the above activities due to knee pain

2. During the past 4 weeks, or since your injury, how often have you had pain?

Never	0	1	2	3	4	5	6	7	8	9	10 Constant
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

3. If you have pain, how severe is it?

No pain	0	1	2	3	4	5	6	7	8	9	10 Worst pain
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐ imaginable

4. During the past 4 weeks, or since your injury, how stiff or swollen was your knee?

1 ☐ Not at all
2 ☐ Mildly
3 ☐ Moderately
4 ☐ Very
5 ☐ Extremely

5. What is the highest level of activity you can perform without significant swelling in your knee?

1 ☐ Very strenuous activities like jumping or pivoting as in basketball or soccer
2 ☐ Strenuous activities like heavy physical work, skiing or tennis
3 ☐ Moderate activities like moderate physical work, running or jogging
4 ☐ Light activities like walking, housework or yard work
5 ☐ Unable to perform any of the above activities due to knee pain

6. During the past 4 weeks, or since your injury, did your knee lock or catch?

☐ Yes
☐ No

7. What is the highest level of activity you can perform without significant giving way in your knee?

1 ☐ Very strenuous activities like jumping or pivoting as in basketball or soccer
2 ☐ Strenuous activities like heavy physical work, skiing or tennis
3 ☐ Moderate activities like moderate physical work, running or jogging
4 ☐ Light activities like walking, housework or yard work
5 ☐ Unable to perform any of the above activities due to knee pain

PTO

SPORTS ACTIVITIES:

8. What is the highest level of activity you can participate in on a regular basis?

1 ☐ Very strenuous activities like jumping or pivoting as in basketball or soccer
2 ☐ Strenuous activities like heavy physical work, skiing or tennis

3 ☐ Moderate activities like moderate physical work, running or jogging
4 ☐ Light activities like walking, housework or yard work
5 ☐ Unable to perform any of the above activities due to knee pain

9. How does your knee affect your ability to:

	1 Not difficult at all	2 Minimally difficult	3 Moderately difficult	4 Extremely difficult	5 Unable to do
a. Go upstairs	☐	☐	☐	☐	☐
b. Go downstairs	☐	☐	☐	☐	☐
c. Kneel on the front of your knee	☐	☐	☐	☐	☐
d. Squat	☐	☐	☐	☐	☐
e. Sit with your knee bent	☐	☐	☐	☐	☐
f. Rise from a chair	☐	☐	☐	☐	☐
g. Run straight ahead	☐	☐	☐	☐	☐
h. Jump and land on your involved leg	☐	☐	☐	☐	☐
i. Stop and start quickly	☐	☐	☐	☐	☐

FUNCTION:

10. How would you rate the function of your knee on a scale of 0 to 10 with 10 being normal, excellent function and 0 being the inability to perform any of your usual daily activities which may include sports?

A. FUNCTION PRIOR TO YOUR KNEE INJURY:

Cannot perform daily	0	1	2	3	4	5	6	7	8	9	10 No limitation in
daily activities	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐ activities

B. CURRENT FUNCTION OF YOUR KNEE:

Cannot perform daily	0	1	2	3	4	5	6	7	8	9	10 No limitation in
daily activities	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐ activities

Thank-you for completing this questionnaire

Please Insert the date when you completed this form ..... / ..... / ..……..
and return in the pre-paid envelope together with your other forms

For trial staff to complete:

Date Entered ..... / ..... / ..……..

Please enter this data into the ACTIVE database (if available) and post a copy of the form together with copies of the other forms from this assessment to the ACTIVE Trial Office, ARC, RJAH Orthopaedic Hospital, Oswestry. SY10 7AG. Please ensure that all original forms are securely filed.

Cincinnati Knee Rating

APPENDIX 6

FORM IDENTIFICATION Pre-rand / 3mt / 6mt / 1yr / 2yr / 3yr / 4yr / 5yr / 6yr / 7yr / 8yr / 9yr / 10yr *(circle as appropriate)*

ACTIVE Trial No. ☐☐☐☐ Patient's Initials …… Patient's DoB ..... / ..... / ……..

1. Sports Activity Scale

Please tick one of the boxes below to indicate your current level of sports activity:

Level I

I take part 4-7 days a week in sports involving

1 ☐ Jumping, hard pivoting (e.g. basketball, volleyball, rugby, gymnastics, circuit training, football)

2 ☐ Running, twisting, turning (e.g. tennis, squash, badminton, hockey, skiing, golf, rock climbing, hill walking)

3 ☐ No running, twisting, jumping (e.g. cycling, swimming, rowing)

Level II

I take part 1-3 days a week

4 ☐ Jumping, hard pivoting (e.g. basketball, volleyball, rugby, gymnastics, circuit training, football)

5 ☐ Running, twisting, turning (e.g. tennis, squash, badminton, hockey, skiing, golf, rock climbing, hill walking)

6 ☐ No running, twisting, jumping (e.g. cycling, swimming, rowing)

Level III

I take part 1-3 times/month

7 ☐ Jumping, hard pivoting (e.g. basketball, volleyball, rugby, gymnastics, circuit training, football)

8 ☐ Running, twisting, turning (e.g. tennis, squash, badminton, hockey, skiing, golf, rock climbing, hill walking)

9 ☐ No running, twisting, jumping (e.g. cycling, swimming, rowing)

Level IV

I do not take part in any sports

10 ☐ I perform activities of daily living without problems

11 ☐ I have moderate problems with activities of daily living

12 ☐ I have severe problems with activities of daily living: on crutches, full disability

2. Activities of Daily Living Function Scales

I do the following:

1. Walking
tick one box

1 ☐ normal, unlimited

2 ☐ some limitations

3 ☐ short distance only without support

4 ☐ need to use stick/crutch even for short distances

2. Stairs
tick one box

1 ☐ normal, unlimited

2 ☐ some limitations

3 ☐ only 11-30 steps possible

4 ☐ only 1-10 steps possible

3.Squatting/kneeling
tick one box

1 ☐ normal, unlimited

2 ☐ some limitations

3 ☐ only 6-10 possible

4 ☐ only 0-5 possible

PTO

3. Sports Function Scales

1. Straight running *tick one box*	**2. Jumping/landing on affected leg** *tick one box*	**3. Hard twists/pivots** *tick one box*
1 ☐ fully competitive	1 ☐ fully competitive	1 ☐ fully competitive
2 ☐ some limitations, guarding	2 ☐ some limitations, guarding	2 ☐ some limitations, guarding
3 ☐ definite limitations, half speed	3 ☐ definite limitations, half speed	3 ☐ definite limitations, half speed
4 ☐ not able to do	4 ☐ not able to do	4 ☐ not able to do

Thank-you for completing this questionnaire

Please Insert the date when you completed this form ..... / ..... / ..……..
and return in the pre-paid envelope together with your other forms

For trial staff to complete:

Date Entered ..... / ..... / ..……..

Please enter this data into the ACTIVE database (if available) and post a copy of the form together with copies of the other forms from this assessment to the ACTIVE Trial Office, ARC, RJAH Orthopaedic Hospital, Oswestry. SY10 7AG. Please ensure that all original forms are securely filed.

EUROQOL EQ-5D

FORM IDENTIFICATION Pre-rand / 3mt / 6mt / 1yr / 2yr / 3yr / 4yr / 5yr / 6yr / 7yr / 8yr / 9yr / 10yr *(circle as appropriate)*

ACTIVE Trial No. ☐☐☐☐ Patient's Initials …… Patient's DoB ..... / ..... / ……..

By placing a tick in one box in each group below, please indicate which statement best describes your own health state today.

Do not tick more than one box in each group.

MOBILITY

I have no problems walking about	☐	1
I have some problems in walking about	☐	2
I am confined to bed	☐	3

SELF-CARE

I have no problems with self-care	☐	1
I have some problems washing or dressing myself	☐	2
I am unable to wash or dress myself	☐	3

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

I have no problems with performing my usual activities	☐	1
I have some problems with performing my usual activities	☐	2
I am unable to perform my usual activities	☐	3

PAIN/DISCOMFORT

I have no pain or discomfort	☐	1
I have moderate pain or discomfort	☐	2
I have extreme pain or discomfort	☐	3

ANXIETY/DEPRESSION

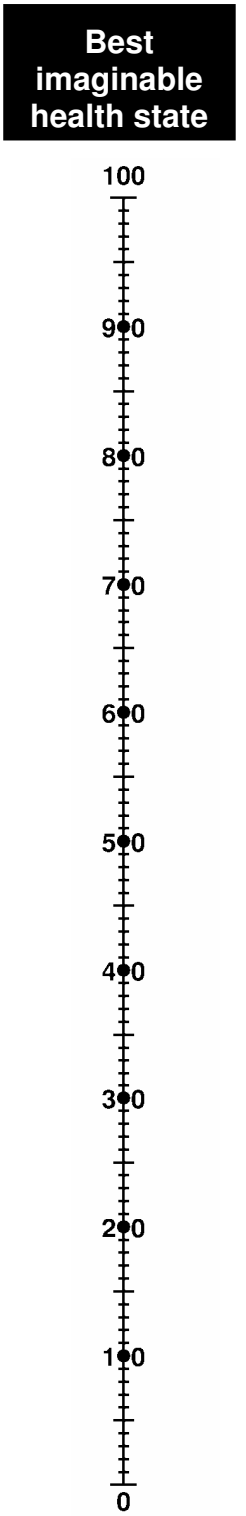
I am not anxious or depressed	☐	1
I am moderately anxious or depressed	☐	2
I am extremely anxious or depressed	☐	3

PTO

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked by 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is.

Your own health state today



Thank-you for completing this questionnaire.

Please Insert the date when you completed this form

..... / ..... / ……..

and return in the pre-paid envelope together with your other forms

For trial staff to complete:

Date Entered ..... / ..... / ……..

Please enter this data into the ACTIVE database (if available) and post a copy of the form together with copies of the other forms from this assessment to the ACTIVE Trial Office, ARC, RJAH Orthopaedic Hospital, Oswestry. SY10 7AG. Please ensure that all original forms are securely filed.

ACTIVE

RESOURCE USAGE QUESTIONNAIRE

This questionnaire aims to explore the costs involved in having a knee cartilage defect. You may like to refer to your knee diary so that you can answer all the questions as accurately as possible. The questions refer to the period since your knee surgery which should be approximately 2-3 months. You should not include the period while you were in hospital having your knee surgery for the ACTIVE trial. If you have difficulty with answering any of the questions please give the best answer you can. The information will be treated as confidential.

VISITS TO THE HOSPITAL

Q1 Since your trial surgery have you been to the hospital about your knee?

Yes ☐ No ☐ (if "no" go to Q9)

Q2 If yes, have you had any additional surgery (e.g. an arthroscopy) on your knee or an injection for your knee since your trial surgery?

Yes ☐ No ☐ (if "no" go to Q4)

If yes, please complete the details below:

	Type of procedure (please name/describe)	**Did you stay overnight?**	**How many nights?**
Surgery 1		No ☐ Yes ☐	
Surgery 2		No ☐ Yes ☐	
Surgery 3		No ☐ Yes ☐	

Q3 For any surgery you had, please indicate how it was paid for:

	Who paid for your treatment?
Surgery 1	NHS ☐ myself/relative ☐ insurance ☐ employer ☐
Surgery 2	NHS ☐ myself/relative ☐ insurance ☐ employer ☐
Surgery 3	NHS ☐ myself/relative ☐ insurance ☐ employer ☐

Q4 Since your trial surgery have you had your knee x-rayed or scanned?

No ☐ Yes ☐ (**If yes**, please complete the details below)

	If yes, how many times?	**Who paid for your treatment?**
x-ray		NHS ☐ myself/relative ☐ insurance ☐ employer ☐
MRI scan		NHS ☐ myself/relative ☐ insurance ☐ employer ☐

ACTIVE

Q5 Since your trial surgery have you seen an **Orthopaedic Surgeon** for an outpatient clinic appointment at a hospital because of your knee?

No ☐ Yes ☐ **If yes**, how many times? ____

Q6 Since your trial surgery have you visited a hospital **for appointments to see any other staff** because of your knee?

No ☐ Yes ☐ (**If yes**, please complete below)

Other hospital staff seen In last 2-3 months	**How many times?**	**Who paid for your treatment?**
Physiotherapist		NHS ☐ myself/relative ☐ insurance ☐ employer ☐
Occupational therapist		NHS ☐ myself/relative ☐ insurance ☐ employer ☐
Other staff *(please specify below)*		
		NHS ☐ myself/relative ☐ insurance ☐ employer ☐

Q7 When you visited the hospital since your trial surgery did someone come with you, for example your spouse/partner, a relative or friend?

Yes ☐ No ☐

Q8 When you last visited this hospital how many miles did you travel in total? (also write where you travelled from and to)

_____ miles for one round trip from _____ to _____

VISITS TO OR FROM GENERAL PRACTICE OR OTHER NHS TREATMENT OUTSIDE THE HOSPITAL

Q9 Since your trial surgery have **you visited your GP** or other staff in the GP surgery or the community (e.g. physiotherapy in another community facility) because of your knee?

No ☐ (**If no**, go to Q11) Yes ☐ (**If yes,** please complete below)

	How many times?
GP	
Practice Nurse	
Physiotherapist	
Other staff *(please specify below)*	

Please turn over the page

ACTIVE

Q10 When you visited the General Practice since your trial surgery did someone go with you, for example your spouse/partner, a relative or friend?

Yes ☐ No ☐

Q11 Since your trial surgery have you **been visited at home** by your GP, or any other NHS health professional because of your knee?

No ☐ Yes ☐ (**If yes,** please complete below)

	How many times?
GP	
Practice Nurse	
District Nurse	
Community Physiotherapist	
Other staff *(please specify below)*	

Q12 Since your trial surgery have you had a **telephone consultation with your GP**, or any other NHS health professional because of your knee?

No ☐ Yes ☐ (**If yes,** please complete below)

	How many times?
GP	
Practice Nurse	
Other staff *(please specify below)*	

OTHER PROFESSIONALS SEEN PRIVATELY

Q13 Since your trial surgery have you seen any professionals privately because your knee?

No ☐ Yes ☐ (**If yes,** please complete below)

	How many times?	**Total cost?**	**Who paid for your treatment?**
Physiotherapist		£	myself/relative ☐ insurance ☐ employer ☐
Complementary therapist (e.g. acupuncturist, reflexologist)		£	myself/relative ☐ insurance ☐ employer ☐
Other professional *(specify below)* *e.g. osteopath*			
		£	myself/relative ☐ insurance ☐ employer ☐
		£	myself/relative ☐ insurance ☐ employer ☐

ACTIVE

MEDICATION

Q14 Since your trial surgery have you taken any medication for your knee?

No ☐ Yes ☐ **If yes**, please complete below. For the last column, if you paid for prescriptions yourself please estimate the total cost for the last 2-3 months since your trial surgery.

Name of medication *(can include tablets, cream, mixture)*	Was this prescribed by the doctor (Doc) or bought over the counter? (OTC) *(delete one)*	**Strength** *e.g. 300mg*	**Dose** How many tablets did you take at a time? *(e.g. 2 tablets)*	**Times per day** *e.g. twice per day*	**Duration** How long have you used this in the last year? *(e.g. all year; 1 month; 2 weeks)*	**Cost to you** How much did you spend on each medication? *(e.g. £30)*
	Doc / OTC					£
	Doc / OTC					£
	Doc / OTC					£
	Doc / OTC					£

ADDITIONAL COSTS BECAUSE OF YOUR KNEE

Q15 Since your trial surgery have you incurred any other costs because of your knee? *e.g. paid for help with work/jobs you couldn't do because of your knee or bought any aids and appliances to help with your knee (e.g. recliner chair)*

No ☐ **Yes** ☐

If yes, what were they for and how much did you spend? In the table below please write the purpose of these costs and an estimate of the amount of money you spent since your trial surgery

Purpose ***(e.g. had to employ a gardener because of my knee / Item (e.g. bought a chair)***	Amount spent ***(e.g. £500)***
	£
	£
	£

EMPLOYMENT

Q16 What is your current work situation?

1 Employed / self-employed full-time ☐ 2 Employed / self-employed part-time ☐

3 Homemaker ☐ 4 Student ☐

5 Unemployed ☐ 6 Retired ☐

7 Voluntary work ☐

8 Unable to work/claiming disability benefit because of knee ☐

9 Other (please specify): _____

Please turn over the page

ACTIVE

Q17 If you are in paid work/self-employed what is your job? (please give title and description)

_____

_____

Q18 How many hours per week are you <u>currently</u> in paid employment or are self-employed?

_____ hours per week

Q19 Since your trial surgery how many days and months have you had to take off work <u>because of your knee?</u>

*(*your knee diary may help you*)*

_____ days **and** _____ months

Q20 If your spouse/partner, a relative or friend accompanies you to hospital or General Practice visits, or helps you in other ways, is this person/are these people in paid employment?

Yes ☐ No ☐ (continue to question 23)

Q21 **If yes**, how many hours per week do they work?

_____ hours per week

Q22 Since your trial surgery how many days has your spouse/partner, a relative or friend had to take off work <u>because of your knee?</u>

_____ days

Q23 Has your work situation now changed <u>because of your knee?</u>

No ☐ Yes ☐ (**If yes**, please complete below)

Changes in my work because of my knee	
1 Working fewer hours per week because of my knee	No ☐ Yes ☐
2 Doing lighter, less physically demanding work because of my knee	No ☐ Yes ☐
3 A change in occupation because of my knee	No ☐ Yes ☐
4 Less job security now because of my knee	No ☐ Yes ☐
5 Reduced income because of my knee	No ☐ Yes ☐
7 Have been made redundant because of my knee	No ☐ Yes ☐
8 Other (please state)	No ☐ Yes ☐

Thank you for your help.

Please check you have answered all the questions before returning this pack.

ACTIVE

SERIOUS ADVERSE EVENT FORM

For the purpose of this study a "serious" adverse event is one which ocurs within one year of the end of treatment for the affected knee and is either:

Deep vein thrombosis, a fall causing injury, infection to the knee joint

Or

Causes death, hospitalisation (or extension to hospital stay), persistent or significant disability, permanent impairment of function, or treatment to prevent permanent impairment of function.

Or

An important medical event that, based on appropriate medical judgement, may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

Please report immediately any serious events by telephoning the Trial Office on +44 (0)1691 404142 and giving the following information:

Patients Full Name: ……

Date of Birth: …… Hospital Number: ……

Responsible Doctor: ……

ACTIVE Trial Number: ……

Date event started: ……

Outcome (e.g. fatal, recovered, continuing) ……

Details of adverse events (please attach copies of relevant reports)

……

……

……

Did the event require hospitalisation? Yes ☐ No ☐

Do you believe this event is related to the treatment? Yes ☐ No ☐

If yes please give reasons why you consider the event to be treatment-related:

……

……

……

Name of person making report (please print) ……

Telephone No:…….. Today's date:……..

When you have made the telephone call, please FAX this form (with copies of any relevant reports) to:

ACTIVE Clinical Trials Office
Robert Jones & Agnes Hunt Orthopaedic Hospital, Oswestry, Shropshire, SY10 7AG. **Fax: 01691 404170**

YOUR JOURNEY THROUGH THE TRIAL

Stage 1: Initial invitation
During your appointment at the outpatient clinic the Orthopaedic Consultant decided you might be suitable for the trial and described the treatment options to you. You were given this Patient Information Leaflet to take home.

Stage 2: Informed consent
Within 3 months prior to your surgery date you attend an appointment at the hospital with the study coordinator who describes the trial to you and answers any queries you have. You also have an opportunity to speak to the Orthopaedic Consultant again if you wish. If you decide to participate in the trial you will give written informed consent. This stage may coincide with Stage 3.

Stage 3: Pre-randomisation assessment
You attend the clinic prior to your operation where a physiotherapist will assess you to find out how you are affected by your knee condition. You will also be asked to spend about 20 minutes filling in some questionnaires about your knee condition and will receive a diary to take home. This assessment may coincide with your routine pre-operative assessment.

Stage 4: Treatment allocation
The study coordinator will let you know which treatment you were randomly allocated to receive.

Stage 5: Your operation
You have your knee operation. If you are having the cell grafting option you have a second operation at least 3-4 weeks later. You receive a rehabilitation advice leaflet and will see a physiotherapist locally for up to six weeks.

Stage 6: Follow-up over ten years
After your operation you attend the usual follow-up clinics and see the surgeon as appropriate. A physiotherapist will assess your progress and will ask you to fill in the study questionnaires. These clinic visits will be at 2-3 months, 6 months and 12 months after your operation.

After Stage 6 you will be contacted annually to complete the questionnaires for the trial and at 3, 5 and 10 years after your operation you will attend the hospital to be assessed by the physiotherapist.

ACTIVE

Autologous
Chondrocyte
Transplantation /
implantation
Versus
Existing treatments

www.active-trial.org.uk

Patient Information Leaflet

For individuals invited to take part in the trial

Version 3.1 February 2008

ACTIVE

Cartilage repair by autologous chondrocyte implantation (CARTILAGE CELL GRAFTING)

ISRCTN 48911177

INTRODUCTION

You have been invited to take part in a research study. It is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. If there is anything that is not clear or if you would like more information, please ask us. Take as much time as you need to decide whether or not you wish to take part.

PURPOSE OF THE STUDY

Defects in the cartilage covering the bones of the knee do not heal by themselves. A technique to treat cartilage defects called autologous chondrocyte implantation (also known as ACI or cartilage cell grafting) was developed in Sweden and has been used on many patients in the UK, and US. This treatment appears to have been successful in treating many patients but has not yet been tried and tested in a formal trial. A newer version of ACI has been developed, known as matrix-assisted ACI (MACI) which is technically easier for the surgeon to perform and slightly less invasive than the traditional technique. Your surgeon will discuss with you which type of ACI therapy he plans to use.

WHY HAVE I BEEN INVITED?

You have been invited to take part in the trial because you are still getting symptoms from the defect in your knee cartilage, even though you have had surgical treatment for it in the past. We aim to recruit at least 420 patients in the UK and 60 patients in Norway.

DO I HAVE TO TAKE PART?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information leaflet to keep and will be asked to sign a consent form. You would still be free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or not to take part, will in no way affect the standard of care you receive.

Thank you for reading this.

You will be given a copy of this INFORMATION LEAFLET and if you agree to take part, a copy of the signed consent form to keep. Further information about the ACTIVE trial is available on the website: www.active-trial.org.uk

CONTACT FOR FURTHER INFORMATION

Local Coordinator

.....

or Local Principal Investigator

.....

or Chief Investigator
Professor James Richardson
Robert Jones & Agnes Hunt Orthopaedic Hospital NHS Trust
Tel: Janet Morris (sec) 01691 404386

or Trial Manager
Dr Heather Smith
Robert Jones & Agnes Hunt Orthopaedic Hospital NHS Trust
Tel: 01691 404142

RISKS AND BENEFIT
If you are allocated to the cartilage cell grafting group this involves a 2-stage procedure, so you will have two operations under general anaesthetic. In addition to the normal risks of knee surgery there is a small risk that you may experience an allergic reaction to a substance used in the cell transplantation. However, this reaction is very rare. We hope that whichever treatment you have will help you. However, this cannot be guaranteed. The information we get from this study may help us to recommend the best course of action for patients like you in the future.

As with other research trials of this kind, should taking part in this research project harm you, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms would be available to you.

CONFIDENTIALITY
We will notify your GP that you are participating in the trial. All information that is collected about you during the course of the research will be entered into the ACTIVE Trial database by study staff and kept strictly confidential. We will need to access your hospital records so that we can collect information on any subsequent surgery or treatment you have on the same knee. If you have the cell grafting treatment your cells will only be used for your treatment, they will not be stored and used for any other purpose.

WHAT HAPPENS TO THE RESULTS?
The results will be regularly reviewed by an independent Data Monitoring and Ethics Committee. The Committee can stop the study if it is clear that any group of patients is being disadvantaged. At the end of the study the results will be published. You will not be identified in any way.

WHO FUNDS THE STUDY?
The Medical Research Council is funding the research costs of the study. None of the doctors looking after you will be paid for including you in the study.

The North Staffordshire Multicentre Research Ethics Committee has approved this study.

WHAT HAPPENS IF I DO DECIDE TO TAKE PART?
Sometimes if we do not know what is the best method of treatment for patients, we need to make comparisons. If you do decide to take part in the trial you will be put into one of two groups. One group will have the cartilage cell grafting treatment and the other group will receive the most appropriate alternative treatment. The groups will be allocated by computer, i.e. by random chance so there will be a 50:50 chance as to which group you will be in. You will have a full assessment of your knee and be asked to complete questionnaires about your knee function and how it affects your quality of life.

If you are allocated to the **cartilage cell grafting group**, you will have a 2-stage operation. Both operations will be carried out under general anaesthetic. The first operation is keyhole surgery during which a small sample of healthy cartilage is taken from the knee to a laboratory for the cells to be grown. The cells are grown in a sterile medium with growth factors or in a medium containing your own blood. After 3-5 weeks, there should be sufficient cells to transplant back into the cartilage defect in your knee. If your own blood is used in the medium then we will take 100ml of your blood (about half a cup full) before the first operation.

At the second operation the knee is opened and any loose cartilage is removed from the defect and a patch is stitched over it. The patch will either be periosteum (the membrane which covers the surface of your bones) or it will be a collagen membrane. If the patch is periosteum, this is removed from your shin through a small additional incision just below your knee. Sometimes the periosteum thickens and a further operation may be required later to reduce the thickening once the cells have regenerated. A newer procedure, in use for 9 years, is a patch made from pig collagen (a fibrous protein found in skin and cartilage). One advantage of this is that an additional incision is not required so you will not have the possible discomfort in your shin. However there has not yet been a long-term trial of this type of patch in comparison with periosteum.

The cells grown in the laboratory are then injected into the defect behind the patch and the knee is closed with sutures. If you are having MACI the cells are grown on collagen membrane in the laboratory, and then the membrane is secured over the defect in your knee using a tissue fibrin sealant without using stitches unless they are necessary.

If you are allocated to the **alternative treatment group** your surgeon will discuss the treatment options with you before selecting one. These

treatments are debridement, microfracture/drilling, or mosaicplasty. They are all carried out under general anaesthetic and have been in use for 5-10 years. A newer treatment called AMIC (Autologous Matrix Induced Chondrogenesis) is also an alternative option in the trial. AMIC is similar to a standard microfracture except that it also involves attaching a membrane (made from pig collagen) over the defect to keep the blood in the damaged area of cartilage. Your surgeon will explain the alternative treatments in full and together you can decide which one is best for you.

BLOOD TESTING

All patients who have cell treatments in the UK must have a blood test to show that they are HIV, hepatitis B, hepatitis C, and syphilis negative. You may also be tested for human lymphotrophic virus (HTLV I & II). For these tests, 8ml (about 2 teaspoons) of your blood will be needed and this is taken either on the day you give consent to enter the trial or at the first stage of ACI. If you have a positive result you may not be able to have cell therapy and your surgeon will discuss this with you. Since 1994 the Association of British Insurers has stated that a negative HIV test does not affect an insurance application. However, if you test positive for HIV your ability to take out life insurance or a mortgage will be affected. Counselling will be available to you before and after the test if you wish.

WHEN WILL I KNOW WHAT GROUP I WILL BE IN?

When you have decided to participate and have signed a consent form you will be registered for the trial. You may be randomised at this stage and will be informed of which treatment group you have been allocated to. If your treatment is expected to be delayed for more than 6 months, you will be randomised and allocated to a group nearer the time of your operation, and you will be informed as soon as this happens.

HOW LONG WILL I BE IN HOSPITAL?

Debridement or drilling and cartilage grafting Stage-1 are usually undertaken as a day-case procedure. Microfracture and AMIC generally require a 1 day stay in hospital while mosaicplasty or cartilage grafting Stage-2 generally require a 2 day stay in hospital. It may also be necessary for you to stay in hospital the night before any of these procedures. Following microfracture, AMIC and Stage-2 ACI a special machine will be fitted to your leg to keep the knee moving while you are in bed but you will not need to stay in bed all the time while in hospital.

WHAT HAPPENS AFTER SURGERY?

Whichever group you are in, you will have the standard physiotherapy and rehabilitation programme that is best for the treatment you received.

After you are discharged you will not be required to attend any further physiotherapy but you will be expected to do your best to follow your recommended programme. Generally, crutches are needed initially, and this may vary from 1 week to 2 months depending on your treatment. Rehabilitation following the cartilage grafting treatment is likely to be slower than the other treatments because the cells need time to generate repair tissue. You should avoid driving for 7 weeks but how long you are off work will depend on the nature of your employment. If your work is very strenuous, you may be off for several months. If you wish to resume high contact sports such as rugby, the recommended rehabilitation period is approximately 12 months but the surgeon will advise you on this before you decide whether to take part in the trial. All patients, whichever treatment they receive, will be given a follow-up appointment 2 or 3 months after surgery and again at 6 months and at 1 year after surgery. This will give your surgeon a chance to see how you are progressing. On each occasion you will be asked to complete some questionnaires and your knee function will be measured by a research assessor who will not know which treatment you had. It is important that you do not tell the assessor what treatment you had, and that you wear a stocking (which will be provided) to cover both your knees so the assessor cannot be influenced by the knowledge of which treatment you have had.

Because we want to compare the long-term outcome of the treatments we will ask you to return to the clinic 3 years, 5 years and 10 years later. This will also alert the surgeon to any problems you may have, whichever treatment you received. We also ask that you agree to let us contact you by post, phone or e-mail on one occasion each year for 10 years so we can check on your progress. Although this sounds like a long time, your cooperation is vital to the success of the trial so it is very important that we can remain in contact with you. If you have difficulty getting to the hospital for a follow-up visit at the proper time, the assessor may be able to arrange to visit you at home.

You will not be asked to take any special medication except that which is normally necessary for your surgery. After you are discharged you will be able to take any other medication that is prescribed or recommended for you. You will not be prevented from having any further treatment on your knee if your condition warrants it, whichever group you are in.

A schedule of your journey through the trial is presented on the back page of this leaflet.

APPENDIX 11

Hospital headed paper

ACTIVE

Autologous
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Transplantation/
Implantation
Versus
Existing treatments

PATIENT CONSENT FORM

Study Number: ISRCTN 48911177 Centre Name: .....

Principal Investigator: .....

Please initial the boxes

1. I confirm that I have read and understand the information sheet dated February 2008 (version 3.1) for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that sections of any of my medical notes may be looked at by responsible individuals from the trial team where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐

5. I agree to take part in the above study. ☐

_____	_____	_____
Name of Patient	**Date**	**Signature**
_____	_____	_____
Name of Person taking consent	**Date**	**Signature**

Name & address of Patient's GP:

.....

Postcode:..... **Tel. No**: .....

Three copies of this consent form are needed:
Top (white) copy to be kept in the patient notes
Yellow copy to be kept by the patient
Pink copy to be forwarded to the study coordinator

APPENDIX 12

ACTIVE

www.active-trial.org.uk

Doctor:
Practice:

Patient Name ..... **Date Randomised** ..... / ..... / .....

Date Of Birth ..... / ..... / ..... **Active Trial No.** .....

Hospital No. .....

Dear Dr

Your above named patient has agreed to take part in ACTIVE, a randomised trial of different surgical procedures for a chondral or osteochondral defect in the knee in which we, and many other centres in the UK, are collaborating.

The trial aims to compare the long-term benefits and costs of autologous chondrocyte implantation (ACI or cartilage cell grafting) with the "best alternative" from a range of other surgical treatments such as mosaicplasty, microfracture and debridement.

The trial is organised by the Robert Jones and Agnes Hunt Orthopaedic Hospital, Oswestry together with the University of Birmingham Clinical Trials Unit and is funded by the Medical Research Council and supported by the Department of Health.

Patients are eligible for the trial if they have had a previous surgical intervention for the defect more than 6 months ago that has not relieved symptoms. All of the treatment alternatives have been explained to your patient who was randomly allocated the following treatment:

☐ Cartilage cell grafting with periosteum ☐ Cartilage cell grafting with membrane

☐ Debridement ☐ Mosaicplasty ☐ Microfracture ☐ Drilling ☐ Abrasion ☐ AMIC

Cartilage cell grafting requires two operations approximately 3-5 weeks apart. In the first stage (day case), a small sample of cartilage is removed from the knee, cells are removed and amplified in the laboratory. At the second stage (2 day in patient stay) the cells are transplanted back into the knee and retained in place either by a patch of periosteum removed from the shin, or by a porcine collagen patch. Mosaicplasty, the transplant of a chondral plug from a non-load bearing area of the knee into the defect also necessitates a 2-day in patient stay. Microfracture and AMIC usually requires a 1-day in-patient stay while debridement and drilling are usually carried out as day cases.

PTO

APPENDIX 12

Following surgery your patient will follow a rehabilitation programme appropriate for the allocated procedure. There are no requirements or restrictions on medication nor will the patient be prevented from having any further treatment for the same problem if that becomes necessary. Follow up will comprise assessment of knee function by an observer who has no knowledge of the treatment allocation, and by self-assessment questionnaires completed by the patient. The follow-up will take place at intervals in the outpatient clinic, and by post, for 10 years. No additional invasive tests or radiology are required.

If you require any further information about the trial please contact me or the study co-ordinator

.....

Yours sincerely,

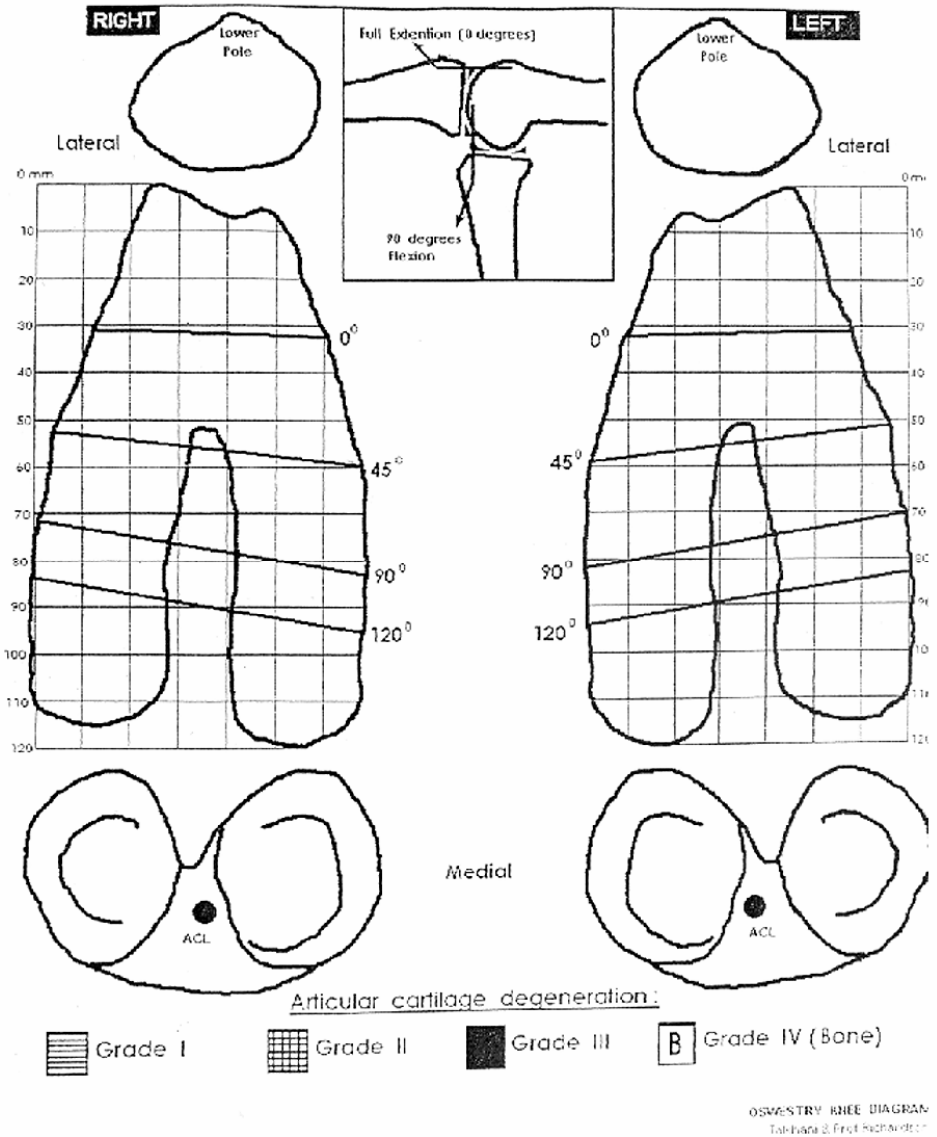
.....

Consultant Orthopaedic Surgeon

Tel:

Treatment Record

Active Trial Number					Patient's Initials:	
Hospital Number:					Date of Birth:	Sex: M / F
NHS Number:					Surgeon:	



ACTIVE **Treatment Record**

PATIENTS'S MEDICAL DETAILS

Where is the defect? (*please tick*)	Medial femoral	Lateral femoral	Trochlear	Patella
Which knee: (*please tick*)	Left:	Right:		
Duration of symptoms:	months/years			

Tick the box if you agree with the following statements:	YES	NO
The patient has generalised OA:		
The patient has untreated malalignment of the patella or an unstable knee:		
The patient had a concurrent total meniscectomy or osteotomy:		
The patient has kissing lesions:		

DETAILS OF ACTUAL TREATMENT

Please tick	Debridement	Abrasion	Drilling	Micro#	AMIC	Mosaicplasty	ACI	MACI	Chondron
Treatment:									

Date of treatment: / / (if ACI date of 1st stage)	If ACI/MACI, date of stage II / /
Actual defect* size before debridement:	(x) cm (or) cm^2
Depth of defect: (bone depth only)	mm
Defect size after debridement:	(x) cm (or) cm^2

*NB if more than one defect give size of largest defect

FOR ACI

Please tick	Medial Ridge	Lateral Ridge	Intercondylar Notch
Biopsy site *(please tick)*			

If periosteum used which site:	Tibial Periosteum:	Femoral Periosteum:
If membrane used which type:	Chondro-Gide:	Other (specify):

Was fibrin sealant used?	YES:	NO:
Number of cells used:	million	
Please score 1 to 10; 10 being the best	Water tightness	Suture security
Self-score for:		

FOR MACI/Chondron

Please tick	MACI (Genzyme)	Chondron	
Type of MACI			
	Medial Ridge	Lateral Ridge	Intercondylar Notch
Biopsy site			
Number of cells used:	million		
Please score 1 to 10; 10 being the best	Self-score for stability:		

ACTIVE **Treatment Record** **Trial No. _____**

FOR MOSAICPLASTY

Instruments used for mosaicplasty:			
Size of donor site	(x) cm (or) cm^2	Number of grafts	
Please score 1 to 10; 10 being the best	Fill	Surface smoothness	
Self-score for			
Comments:			

OSTEOCHONDRAL DEFECTS REQUIRING BONE GRAFTING
(for defects with more than 3mm of bone loss and/or Subchondral bone sclerosis)

Depth of bone loss prior to grafting mm		Depth of bone loss after grafting mm	
Please tick type of graft and whether sandwich technique was used			
	Autologous	Allogenic	Substitute (specify make)	Sandwich method
Type of bone graft				

For All Procedures

If patient did not receive their allocated treatment please give reasons or any other comments:

Please forward one copy of this form to your local trial co-ordinator and keep the original form with the patient's notes.

Copy made for Co-ordinator: YES ☐ NO ☐

Name of Surgeon	
Signed:	Date:

For Study Co-ordinator:
Please post a copy of this form to the ACTIVE Trial Office, ARC, RJAH Orthopaedic Hospital, Oswestry, SY10 7AG. Please ensure that the original form is securely filed.

Utility analysis for NICE based on the SUMMIT trial

Developed for Vericel by Mapi

18 June 2015

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Utility analysis for NICE based on the SUMMIT trial

1. Introduction

NICE has asked Vericel to provide insight into the utilities collected alongside the SUMMIT trial, as part of their multi-technology assessment (MTA) of autologous chondrocyte implantation (ACI) for repairing symptomatic articular cartilage defects of the knee.

During this assessment, a review of the literature was carried out and utilities values were identified from several sources. These included values from Gerlier[1] which concerned utilities that were obtained by a not very well described transformation from the SF-36. In addition, utilities by Clar *et al*[2] were identified which reported a 0.80 utility pre-operatively and a 0.10 gain as a consequence of a successful operation. And finally there were scores obtained by Derrett *et al* which reported pre-operative utility scores of 0.41, increasing to 0.64 post successful ACI. [3]

The Assessment Group chose to use the utilities reported by Gerlier in their cost-effectiveness model and these are shown in Table 1.

Table 1. Gerlier utilities used in the Assessment Group's model

State	*Value*
Before primary repair	0.651
1st year after successful repair	0.760
2nd to 4th year after successful repair	0.810

Review of the model has shown that the model results are sensitive to changes in utilities.

2. The SUMMIT trial

The SUMMIT trial [46] is a prospective, randomised, open-label, parallel-group, multi-centre study, sponsored by Genzyme (Sanofi). The study compared matrix-induced autologous chondrocyte implant (MACI) (N=72) with micro fracture (MF) (N=72) in patients aged 18 to 55 with Outerbridge Grade III or IV focal cartilage defect ≥3.0 cm^2. The co-primary outcomes in the trial were change from baseline to Week 104 in knee injury and osteoarthritis outcome score (KOOS) pain score and KOOS function (sports and recreational activities (SRA)) score. The study was followed by a three-year extension study. Results from both studies have been included in this clinical section of the MACI submission, though only one-year data are available from the extension study.

As part of this trial the EQ-5D was collected alongside this trial at baseline, week 52, 104 and 156 (this last data point as part of the extension study). The EQ-5D was administered as the standard questionnaire including the VAS scale. This brief report only presents findings using the EQ-5D index questionnaire and does not include VAS data.

3. Findings

Patient-level data of the trial were transferred to Mapi for analysis. To estimate the utilities the Dolan algorithm was used, using the UK national tariff. Data from all available patients were used in this analysis. Note that duplicate observations in the dataset were deleted. Patients with missing observations were not considered in the analyses. No imputation was used.

At baseline, consisting of 141 patients, a utility score of 0.484 (SD:0.296) was reported. From Table 2 is clear that the overall utility of all patients increases after the intervention (MACI or MF) and that this increase continues over time, with a difference between year 1 and year 3 of 0.3, which is substantially more that the generally considered minimally significant difference of between 0.05 and 0.08 for UK-index. [5] Thus indicating that there is actual improvement in HRQoL over time.

Table 2. Utilities EQ-5D all patients by visit

VISIT	N Obs	N	Mean	Std Dev	Median
SCREENING	144	141	0.484	0.296	0.620
VISIT 8 WEEK 52	140	139	0.766	0.219	0.796
VISIT 10 WEEK 104	140	140	0.762	0.252	0.778
VISIT 11 WEEK 156	124	124	0.796	0.233	0.796

It is important to note that the difference of 0.282 (year 1) and 0.312 (year 3) includes patients who have not benefited from surgery.

When we consider the utility score of responders (defined as reporting a ≥10 point difference on the KOOS) and non-responders (KOOS improvement less than 10 points) from the entire trial population, a strong statistically significant difference at all three post-intervention time points was observed between these two patient groups. Difference from baseline for responders increases from an impressive 0.32 at year 1, to an increase of 0.38 in year 3, while for non-responders the utility score remains fairly flat with increases ranging from 0.04 (below the significant clinical difference) to 0.09 at year 3.

Table 3. Utilities of responders and non-responders by time period – difference from baseline

Response time	*Response type*	*N Obs*	*N*	*Mean*	*Std Dev*	*Median*	*P value of difference*
Responses at week 52	Non-responder	22	22	0.0437	0.3293	0.0165	0.0003
	Responder	116	112	0.3211	0.3167	0.2765	
Response at week 104	Non-responder	25	24	0.0092	0.1943	0	<0.0001
	Responder	110	108	0.3334	0.3226	0.2730	
Response at week 156	Non-responder	37	35	0.0892	0.2790	0	<0.0001
	Responder	86	85	0.3871	0.2968	0.3090	

Taking this into consideration the utility values observed are shown in Table 4 below.

Table 4. Final utility values using EQ-5D

Time period	*Patient group*	*Utilities*
Pre-operation	All	0.484
Post-op – 1 year	Responders	0.805
	Non-responders	0.528
Post-op – 2 years	Responders	0.817

	Non-responders	0.493
Post-op – 3 years	Responders	0.871
	Non-responders	0.573

Analyses comparing utility scores MACI with MF, i.e. by treatment arm, after the intervention, and thus including both responders and non-responders, only found a statistically significant difference at week 104 though at other time points a clear numerical difference between the two treatment arms was reported as is shown in Table 5 below.

Table 5. Utilities by treatment arm at various time points

Time	*Treatment arm*	*N*	*Mean*	*Std Dev*	*P value*
Responses at week 52	MACI	71	0.7848	0.2113	0.3129
	MF	68	0.7472	0.227	
Response at week 104	MACI	70	0.8051	0.1899	0.0425
	MF	70	0.7188	0.2969	
Response at week 156	MACI	65	0.8131	0.2105	0.3899
	MF	59	0.7769	0.2553	

4. Discussion

A utility score of 0.484 prior to surgery, as obtained from this analysis, is substantially lower than the value of 0.654 obtained from Gerlier, and represents a difference of 0.17, which in utility terms is very substantial. The value of 0.484 is very similar to the findings of the ISPOR abstract reporting the baseline utility scores based on the SUMMIT data, where a value of 0.481 was reported.[6]

This difference in utility between Gerlier and SUMMIT is perhaps caused by the lower severity of patients included in the ChondroCelect trial, the SF-36 data from which were used in the Gerlier study as is shown in Table 6. That said, the utility scores post-

intervention, are remarkably similar. This likely indicates that after surgery, regardless of prior severity, the HRQoL outcome is similar, which is very positive for the (M)ACI intervention.

Table 6. Comparison of SUMMIT and ChondroCelect studies

Parameter	*SUMMIT*		*TIG/ACT/01/2000*	
Treatment arm	MACI	MF	ChondroCelect	MF
Age (years)	34.8	32.9	33.9	33.9
% male	62.5	66.7	61	67
KOOS pain*	37.0	35.5	62.05	
KOOS function *	14.9	12.6	65.03	
Duration of symptoms (years)	5.8	3.7	1.97	1.57
BMI	26.2	26.4	NA	NA
Lesion size (cm2)	4.9	4.7	2.6	2.4
Grade III %	29.2	20.8	18	26
Grade IV %	70.8	79.2	82	74
Prior surgery %			88	77

* The KOOS assesses pain, symptoms, activities of daily living, sport and recreational activities, and knee-related quality of life, with scores of 0 (worst) to 100 (best).

However, this leaves the decision as to which values to use for the pre-operative state. To evaluate the cost-effectiveness of MACI, the values provided in this study should be used as these reflect the patient population in which this treatment is/will be used. Based on Vericel's expert opinion, which is based on their experience with MACI outside the SUMMIT trial, they are of the opinion that the typical patients being considered for (M)ACI are very similar to the SUMMIT trial patients given their lesion size, chronicity of symptoms, aetiology of lesion and number of prior procedures.

When the values from responders and non-responders are considered, we found values similar to those reported in the ISPOR abstract. These minor discrepancies can be explained by the differences in patients with missing values and imputation methods used in the ISPOR analysis, while patients with missing values were not considered in our analysis. This lead to a reported improvement in the ISPOR analysis of 0.352 reported for responders and 0.033 for non-responders at year 2, while in this current analysis we have found improvements of 0.333 and 0.009 respectively at year 2 for these two patient groups. At year 3 values obtained from the current analysis were higher at 0.387 than any of the reported year-2 results, while scores for the non-responders in the current analysis approximated those found in the 2-year ISPOR analysis.

When the analysis by treatment arm, MACI or MF, is considered, it is clear that there is a numerical (and at times statistically significant) difference between treatment arms and therefore it is right that different values should be used for these two treatments in the model rather than identical ones.

Over time, it is clear from this analysis that HR-QoL does not decrease but rather increases, though starting at slightly lower values than currently used in the model and increasing, over time, to values currently used in in the model from year 2 onwards. This should perhaps also be reflected in the Assessment Group's model.

In light of the current utility scores, the Assessment Group may also consider reviewing the utility scores used before and after total knee replacement, as the value prior to total knee replacement seems, at 0.615, high, given that this an intervention of last resort.

5. Conclusion

Based on the evidence presented above, Vericel is of the opinion that there is sufficient evidence available from the SUMMIT trial to change the utility scores that have been used in the Assessment Group's cost-effectiveness model, especially the baseline value and the differences between treatments.

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Autologous chondrocyte implantation in the knee: additional analyses 1st March 2016

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List of abbreviations

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

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

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

Scientific summary

Following the second Appraisal Committee meeting, NICE requested additional work and further analyses from the Assessment Group.

Longer-term results

The first request arose because the trials included under the original scope from NICE, on second and third generation autologous chondrocyte implantation (ACI) provided results only up to 3 and 5 years, and for modelling of cost-effectiveness, longer-term outcome data were desirable. It was decided that longer-term data from the first generation of ACI, which used a periosteal cap (ACI-P), could be used, based on an assumption that data on longer-term outcomes of chondral defect repairs from studies of ACI-P, could be extrapolated to survival of repairs after second generation ACI with a collagen cap (ACI-C) and third generation ACI where chondrocytes are seeded into a collagen matrix (MACI). ACI-P has been superseded by the later generations, as the new techniques were simpler and quicker and the use of periosteum was associated the complexity of harvesting and ensuring a watertight cap, and with overgrowth hypertrophy requiring reoperation and shaving of the graft, and the extra discomfort to patients from these procedures. The collagen cap is much easier to use but does come at an extra cost. The third generation of ACI in which the cells are seeded on to the collagen membrane is quicker still.

It was felt that results from the actual repair of the cartilage defect after ACI-C and MACI would at least be no worse than after ACI-P.

We therefore identified studies reporting longer-term results of ACI (mostly ACI-P), most with over 10 years follow-up. Most were observational studies with no control groups. We did the same for microfracture.

Some of the studies found were excluded for various reasons, including use of forms of ACI that were outwith the remit, such as those using the Hyalograft scaffold. Others had too high rates of concomitant procedures such as tibial osteotomy (which by itself may lead to reduction of pressure on the damaged area and fibrocartilage repair), and long term improvements in pain and functional outcomes).

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Survival analysis – time to failure in longer term studies.

We included six studies of long-term results of ACI, the best of which was by Nawaz and colleagues from Stanmore. It was best because of size (827 – greater than the other studies put together), because

it reflected UK practice (albeit from a centre of excellence), because it provided data from the period 1998 to 2008, on different generations of ACI, and because it provided very useful subgroup data.

The findings of the Nawaz study include;

- ACI graft survival was 78% at 5 years and 51% at 10 years for the whole cohort
- There was no difference between survival rates of ACI-P and ACI-C (combined) and MACI. Most (63%) received MACI
- Outcomes were much poorer in patients who had had previous attempts at cartilage regeneration such as microfracture, with an almost five-fold failure rate (HR for failure 4.72).
- The presence of osteoarthritis also increased failure rates, especially amongst patients with Kellgren-Lawrence grades 2 and 3, amongst whom only 25% had graft survival to 10 years.

We used the Nawaz results as the main input into survival analysis and cost-effectiveness, but also did a sensitivity analysis incorporating five other long-term studies of ACI.

There were few long-term studies of microfracture so it was necessary to construct survival curves based on 5-year data from only three studies. These studies were two trials with 40 and 61 patients, and a large observational study from routine care in the USA with 3,498 patients having MF.

Amongst other analyses, we compared the MF results with the worst performing ACI subgroups from the Nawaz study.

The ACI groups had lower failure rates than the MF cohorts, except for the ACI group with previous attempts at repair or with degenerative change. Data were sparse on results of MF in previously treated patients.

[redacted]

In summary,

- More long-term evidence was available for ACI than for MF
- Treatment failure definitions differed between studies with varying and sometimes unclear relative contributions to overall failure from re-intervention and from inadequate pain/function scores.
- Study data were generally still too short-term. Only one published study allowed an estimate of observed median time to failure.
- Caveat: Immaturity of failure data necessitated parametric modelling beyond observed data so as to predict life-time failure. Such extrapolations assume that curves based on the observed data will continue.
- Most participants in most study populations had experienced intervention(s) prior to enrolment; where evidence was reported it appears many types of pre-intervention had been tried. Two ACI studies with Kaplan-Meier survival analyses extending to at least 10 years reported that treatment failure was far more frequent in patients who had experienced prior-intervention(s). This reduced the likelihood of success after ACI and makes extrapolation of results from older studies to ACI as first procedure, rather pessimistic.
- According to information criteria and visual goodness of fit, the best fits of long term failure after ACI were usually characterised by models that when extrapolated beyond the observed data indicated gradually decreasing hazard (probability of failure decreasing with time).
- Conversely good fits to limited data available for MF were characterised by models that indicated linearly increasing hazard (probability of failure increasing with time).

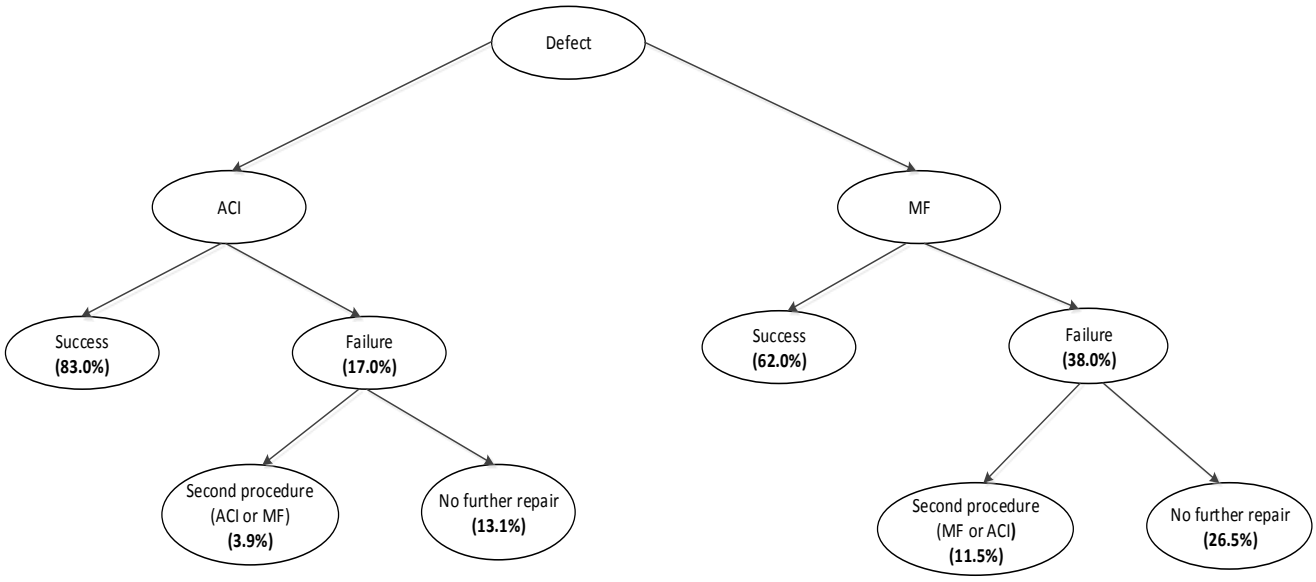
Economic analysis

We used data from the long-term studies in a new base case analysis, using the whole Nawaz cohort results for ACI, and pooling the MF results from three studies. At the request of NICE, we used an implantation cost of £2,396. Also at the request of NICE we omitted the option for MF failure to be followed by another MF. So the options were;

- MF, followed by ACI if another procedure was considered necessary in the short-term. In the long-term, patients would be considered for knee replacement, but most would still be too young for that after MF failure.
- ACI followed by MF if another attempt at repair was necessary
- ACI followed by a second ACI if another attempt at repair was necessary.

For convenience, figure 6 from the first assessment report is reproduced here. The results are only after 3 years, at which time most of those whose first procedure failed, had not had a further attempt at repair.

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



The new base case analysis used MF followed if necessary by ACI, as the lowest cost option, with other options then being compared with that. ACI followed by MF was dominated by ACI followed if necessary by ACI, because of the poor long-term results of MF.

The ICER for ACI as primary procedure compared to MF was around £19,000 – a little less in deterministic analysis, a bit more in probabilistic. A caveat is necessary – the marginal QALY gains were small, at 0.0650 in deterministic and 0.0824 in probabilistic. These equate to around 24 and 30 days of perfect health.

SoBi submitted an offer of a price reduction, which as expected, reduced the ICER to £[redacted] (deterministic). [redacted]

We carried out a range of sensitivity analyses. Firstly we looked at price options. The deterministic ICERs for ACI as first procedure compared to MF were as follow;

- Cost of cells £6,000 – ICER £7,414
- Cost of cells £8,000 – ICER £9,700
- Cost of cells £12,000 – ICER £14,272

Secondly we tested a series of utility assumptions for those whose first repair was not successful but who decided not to have another. In our first assessment report, we assumed that they had had some benefit, and had improved from a utility of 0.654 before the repair to 0.691 afterwards. NICE asked us to assess the effect of the following assumptions for utilities in those in whom repair in unsuccessful but who choose not to have another operation:

- Utility set to the same as failure (0.654) - ICER £15,634
- Utility set to same as success (0.817) – ICER £62,658. This assumption greatly increases utility gain amongst those who do not get good results after MF, and reduces the marginal QALY gains from ACI.
- Utility set to midpoint of success and failure (0.746) – ICER £27,123. This also reduces the marginal QALY gains from ACI as first procedure, because the larger proportion which does not do well after MF, has their utility increased.

The Nawaz study provides very useful data on subgroups;

- Previous attempts at repair, such as microfracture – ICER £38,262. ACI is much less successful if the underlying bone has been damaged.
- Individuals without prior repair attempts – ICER £15,659
- Kellgren grade 0 – no radiological sign of osteoarthritis – ICER £15,618
- Kellgren grade 1- radiological signs of early OA – ICER £17,104
- Kellgren grade 2 – ICER £20,096
- Kellgren grade 3 – ICER £21,207

In a sensitivity analysis, instead of relying on the Nawaz data alone, we tested the effect of pooling six ACI studies and found an ICER of £16,708. Adding a seventh, the ACTIVE trial, gave an ICER of £17,325.

In the first assessment report, we noted an abstract of a study not published in full in which patients with chondral defects were reported to have a baseline utility of 0.484. Vericel provided details from the unpublished study. Using that baseline and their 3-year utility gain would give an ICER of £15,648. The baseline looks surprisingly low for a young group of often sportspeople with only a painful knee, but such injuries can be quite disabling.

SoBi submitted some survival analyses using 5 ACI studies which provided data beyond 5 years. They did not include Nawaz, but did include a study that used the Hyalograft scaffold, which is not a collagen product and therefore was excluded from Assessment group consideration. SoBi did not pool

any MF studies. Their long-term survival of ACI grafts was 70% which reduces the ICER to about £21,000, and to £[redacted] with the PAS price reduction.

Research needs

ACI is less successful amongst people with osteoarthritis but ICERs can be in the range usually considered acceptable. However grading osteoarthritis by radiological appearances by the Kellgren-Lawrence method has some problems. Nevertheless ACI may have a place in early osteoarthritis with focal damage – research is needed in this group.

Conclusions

As requested by NICE, we carried out survival analysis based on what data we could find. Caveats are necessary.

There were more long-term studies of ACI than of microfracture. Using longer-term data than were available in the trials, microfracture comes out much less well. However there are few long-term studies of microfracture, and extrapolation beyond observed data is subject to uncertainties. Few microfracture studies report subgroups. The evidence base is much stronger for ACI, but in older studies, most patients had had previous attempts at repair. ACI is less successful after previous attempts at repair. Previous studies may therefore provide a pessimistic assessment.

A key conclusion is that ACI will give better results if used as first repair procedure.

A range of economics analyses produced ICERs that might be considered acceptable by NICE. Of note is that ICERs in early osteoarthritis also appeared acceptable, but the clinical evidence base is much sparser than for chondral defects.

1 Background

Following the second Appraisal Committee meeting, NICE requested additional work and further analyses from the Assessment Group.

In the assessment report, we focused on the second and third generations of ACI, on the assumption that the first generation, ACI-P with the periosteal cap, had been superseded by the later generations, because the new techniques were simpler and quicker and the use of periosteum was associated the complexity of harvesting and ensuring a watertight cap, with overgrowth hypertrophy requiring reoperation and shaving of the graft, and the extra discomfort to patients from these procedures. The collagen cap is much easier to use but does come at an extra cost. The third generation of ACI in which the cells are seeded on to the collagen membrane is quicker still.

Because the second (ACI-C) and third (MACI) generation of ACI are fairly recent developments, we lack long-term data on their success rates. The TIG-ACT trial of ChondroCelect has 5-year follow-up [1] but the SUMMIT trial of MACI has so far only published 2-year results in full[2] with 36 month results in an abstract.

NICE therefore requested a review of all studies that provide long-term outcomes for ACI and microfracture, including both RCTs and observational studies, and all generations of ACI. In practice, if we define long-term as more than 5 years, the ACI evidence comes from first generation ACI, ACI-P..

There is some evidence to support extrapolating long-term outcomes after ACI-P to later generations. Gooding and colleagues[3] compared first generation ACI-P with second generation ACI-C, and found them similar in terms of repair quality. There is no evidence that ACI-P has any advantages over ACI-C or MACI. (There was once a theory that the periosteal cap might promote chondrocyte function.) So it seems reasonable to assume that data on longer-term outcomes of chondral defect repairs from studies of ACI-P, can be extrapolated to survival of repairs after ACI-C and MACI. Niemeyer 2014[4] compared ACI-P with ACI-C with 23 patients with each, matched for defect size and site, and age. Lysholm and IKDC scores were better with ACI-C: Lysholm 63 versus 76, p = 0.03; IKDV 76 vs 68, p = 0.023) but failures rates (defined as need for re-intervention) were the same by 10 years – 4 of 23 in each group (17%).

Goyal and colleagues[5] carried out a meta-analysis to compare first generation ACI with later generations, but found only three relevant studies, one of which was Gooding 2006.[3] Niemeyer 2014[4] was not included. Goyal and colleagues[5] concluded that there was only weak evidence that ACI-C

was any better than ACI-P because studies were only up to 2 years duration and numbers were small. However, ACI-C was clearly no worse than ACI-P.

ACI-C was compared with MACI in one randomised trial from the Stanmore group. Bartlett and colleagues[6] randomized 91 patients to ACI-C or MACI. Follow-up was only for one year. The MACI group did better in symptoms, but the ACI-C group did better in cartilage quality. Despite randomization, the ACI-C group had longer duration of symptoms (119 months versus 88) and a higher proportion of previous failed procedures (20% vs 4%) both of which are associated with poorer outcomes. However the surgical team had longer experience of ACI-C than MACI.

In passing, it is worth noting the long duration of symptoms in many of the trials, and that this means that the results are likely to be worse than if ACI was used much sooner.

We therefore carried out a systematic review of long-term results of MF and ACI, defining long-term as at least 5 years, not restricting study design, and assuming that the survival results of ACI-P could be extrapolated for modelling purposes to ACI-C.

1.1 Methods

Inclusions: studies of any type of ACI that uses periosteal or collagen caps, or collagen matrices. Studies of microfracture, both traditional and capped (autologous matrix-induced chondrogenesis [AMIC]).

Exclusions: studies of other forms of ACI, such as those using fibrin glue or synthetic caps or matrices not using collagen. Trials with fewer than 20 patients per arm. Observational studies with fewer than 40 patients. Studies of < 5 years duration (even if a few patients have duration over 5 years). Trials or case series using drilling or abrasion methods. Studies where over 30% had significant concomitant surgery such as tibial osteotomies, patellar re-alignment, or cruciate ligament repair.[7, 8] Minor concomitant surgery such as partial meniscectomy was allowed.

Search strategy

Searches, as shown in Appendix 1, were run in Ovid Medline and Ovid Embase from 1997 to 15 May 2015. Thereafter weekly auto-alerts in Medline and Embase of these searches were run until the end of 2015 to check for any new potential inclusions.

The searches retrieved 2907 documents; after removing duplicates and animal studies 1833 records remained and the title and abstracts were screened by two authors for inclusions. The full text of 69 articles was checked and 26 articles (21 studies) were included and 43 articles were excluded.

Quality assessment used the NIH checklist for observational studies as shown.[9]

Box 1. NIH Quality Assessment Tool for Case Series Studies NIH

Quality Assessment Tool for Case Series Studies NIH

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the study question or objective clearly stated?			
2. Was the study population clearly and fully described, including a case definition?			
3. Were the cases consecutive?			
4. Were the subjects comparable?			
5. Was the intervention clearly described?			
6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?			
7. Was the length of follow-up adequate?			
8. Were the statistical methods well-described?			
9. Were the results well-described?			
Quality Rating (Good, Fair, or Poor) Fair			
Rater #1 initials:			
Rater #2 initials:			
Additional Comments (If POOR, please state why):			

*CD, cannot determine; NA, not applicable; NR, not reported

1.2 Results

A broad search with no restriction on designs (to capture case series) retrieved an initial 1833 studies, of which 67 were possible inclusions, based on abstracts.

Table 1 shows the included studies. Not all were used in survival analysis. Excluded studies are listed in Appendix 3.

Table 1. Included studies.

Author	Brief description	Quality assessment and used in survival analysis
Asik 2008[10]	Assessment of a series of 90 patients after microfracture. Those having other procedures as well were excluded. Mean follow-up 68 months. No failure data reported. Better results in those treated sooner (< 12 months) after injury, in younger (<35) people, defects < 2 cm^2 and BMI < 25. No data on previous procedures.	Fair, no
Bentley 2012[11]	Long-term (minimum 10 years, range 10-12 yrs) results of the 58 patients in the ACI arm from RCT versus mosaicplasty. (Bentley 2003 JBJS 2003/85B/223-30). Loss to FU 9%, censored at last visit. ACI-P or ACI-C. Long duration of injury before ACI (mean 7 yrs, range 1 to 20) and 94% had had previous surgery such as mF. 175 failure rate - graft failure or re-operation. Mean defect size 4.6cm^2 , range 1 to 10.	Good, subsumed into the Nawaz study in survival analysis but see Discussion
Beris 2012[12]	Case series of 42 patients (45 knees) after ACI-P. Mean defect size 5.3 cm^2 range 2-12. Mean duration 28 months. No data on prior surgery, loss to follow-up or failures.	Poor, no.
Bhosale 2009[13]	Cohort study of first 80 consecutive patients having ACI-P 1996-2002. ACI-only. 87.5%	Fair, no

	previous surgery. Duration of defect not reported. Failures NR. Mean defect size 4.1cm^2, IQR 3-6. If success at 15 months, sustained for up to 8 years.	
Biant 2014[14]	Case series 104 patients after ACI-P (19) or ACI-C (85) in 1998-2001, followed for at least 10 years. Duration defect 7.8 yrs, size 4.8, range 1-25. Loss to FU 4%. Previous surgery in 70% and they had poorer results. Failures in 26% at mean FU 5.7yrs (all by 8yrs), defined as revision of repair or arthroplasty. Results in non-failures good or excellent in 88%.	Good, but subsumed under Nawaz study in survival analysis but see Discussion
Browne 2005[15]	Case series. Clinical outcome of ACI at 5 years in 87 subjects. Defect size 4.9 cm^{2,} duration not reported. Previous failed surgery 70%. In 36%, the ACI was the first performed by surgeon. Of the 87, 62 (70%) improved, six no change, 19 worse.	Fair, no.
Gomoll 2014[16]	ACI in the patella only. Case series of 110. 8% failures, defined as graft failure with pain requiring revision surgery.	Fair, no.
Jungmann 2012[17]	Cohort study of predictors of failure 2 to 12 years after ACI. 26% ACI-P, 57% ACI-C, 17% Bioseed. Failure defined as need for revision surgery. N=413. Prior repairs 70%, with > one 16%. More than one prior repair increased risk of failure fourfold. ACI-P doubled risk of failure vs ACI-C. No association of age or BMI with failure but only 85 had BMI > 30. Duration of defect NR	Fair, used.
Krych 2012[18]	Case series of 48 microfracture patients from comparative study of mosaicplasty and microfracture.	Not used in survival analyses
Knutsen 2007[19]	This RCT of ACI versus microfracture showed no difference. N=80. 5 year follow-up. 23% failure in both arms, defined as need for	Fair, used.

	revision. 93% had had prior repairs. Median duration of defect 3 years. At baseline, people with OA excluded but by 5 years, 34% had Kellgren grade 2 or worse, in their late thirties. Younger patients did better (<30).	
Layton 2015[20, 21]	Layton et al report results of microfracture in a very large observational study of 3,498 patients in the USA. The data were obtained from an administrative claims database. The study has not yet been published in full, but is available as an ISPOR abstract. The authors have provided a copy of the full poster.	Good, yes.
Moseley 2010[22]	Registry-based case series of 72 patients from 35 centres, 24 of which only entered one patient. In 29%, the ACI was the first done by the surgeon. Mean defect size 5.2 cm^2. 36% had had previous attempts at repair. Duration of defect not reported. 21% had concomitant surgery but mostly minor with only one osteotomy. Failure, defined as need for re-operation, occurred in 17%. At 6-10 years, 69% of patients had good results.	Fair to good, yes.
Nawaz 2014[23] Incorporates Rogers 2010[24] with the Briggs series. Also incorporates data from the ACI arm of the Bentley 2012 trial, and the patients in the Biant 2014 study.	Long-term study ACI in 827 patients with mean follow-up 6.2 years (range 2 to 12) after ACI (P or C) in 37% or MACI (63%). 499 had reached 5 years of FU and 366 had reached 8 or more year, making it one of the most useful studies. Mean defect size 4.1$cm^{2,}$ rrange 0.6 to20.8. 34% had had previous cartilage repair surgery, and they were 5 times as likely to fail ACI. Failure was defined as need for further surgery, graft delamination (MRI or arthroscopic) or symptom scores close to or worse than pre-op. Early OA was associated with poorer outcomes – HR for failure 2.1 for Kellgren grade 1, 3.5 for grade 2, and 3.8 for grade 3. Defect size did not affect	Good, yes.

	failure risk.	
Niemeyer 2014[25]	Case series of ACI-P. N = 86 but 16 lost to FU. Duration of defect "several years", mean size 6.5cm^2. 34% prior repair attempts. Some concomitant surgery but mainly partial meniscectomy. 29% had further surgery but not all related.	Good but for 19% drop-out rate
Niemeyer 2014[4]	Matched pair comparison of outcomes of ACI-P versus ACI-C. 23 per group and FU at least 10 years. Same failure rate – 4 (17%) in each group required further surgery including TJR. ACI-C better on Lysholm and IKDC scores. But small study.	Good, no.
Peterson 2010[26]. Includes patients reported in Peterson 2002[27] with chondral injury and 26 of those in Peterson 2003[28]	Long-term follow-up of the Gothenburg patients of Brittberg et al who had had ACI-P at least 10 years before (but range given as 9.3 to 20.7 years) with mean FY 12.8 years. 341 questionnaires sent out and 224 replies (65%) despite many having moved. Lysholm, KOOS etc plus question about whether they would have again – over 90% would. 74% reported better or same, 26% worse. No data on failures requiring reoperation provided. Neither age nor size of lesion affected outcome. Size 5.3cm^2 mean lesion size but some had more than one lesion. So majority had good result 10-20 years later.	Fair, not used
Salzmann 2013[29]	Reoperative characteristic after microfracture of knee cartilage lesions in 454 patients Retrospective chart review Mean follow up duration Failure subjects: 5.0 ± 2.1 Non- failure subjects: 4.4 ± 1.9	Not used in SA
Shive 2015[30] Also Frappier 2014[31]	This study reports a multicentre RCT of microfracture with BST-CarGel versus	Fair, not used

	microfracture alone at 5 years. There was no ACI arm. The trial was of a form of enhanced MF, with a chitosan framework to stabilize the blood clot. At 5 years, there was no difference in clinical outcomes, but the quality of the cartilage filling was better with CarGEL. Whether this would result in later clinical benefits from a longer-lasting repair is not yet known. A cost-effectiveness analysis (Frappier 2014) making assumptions on failure and fill, reported that BST-CarGEL could be cost-saving.	
Solheim 2014 [32](incorporates patients from Solheim 2010[33])	Microfracture treatment of single or multiple articular cartilage defects of the knee: a 5-year median follow-up of 110 patients.	Not used
Steadman 2003[34]	Follow-up of cohort of 72 patients after microfracture for traumatic chondral defects of the knee. Average follow up 11 years, range 7 to 17. Duration of defect mean 3 years, range 9 months to 7 years. Size mean 2.8cm^2. Only 2 failures, which were excluded from study. Of 71 followed for 7 years, 59 had improved, 11 were the same and one was worse. Unusually low failure rate. Patients were selected from a larger (302) group by excluding those with other lesions, degenerative change and concomitant surgery. Note quite small size of lesion and inclusion of children.	Fair, used.
Vanlauwe 2011[1]	Five-year results from the TIG-ACT trial of ChondroCelect versus microfracture dealt with earlier in assessment report.	Good, used in SA.

Comparing results of different studies is not straightforward, because a number of factors influence the results, including;

- Previous attempts at repair – these reduce the chance of success. Most of the older studies had patients who had had unsuccessful previous surgery.
- Size of defect. Large lesions don't do well with microfracture
- Site of defect. For example, ACI appears to be less successful in trochlear lesions. Some studies exclude trochlear lesions (Knutsen 2007 [19])
- Duration of chondral defect
- Surgical experience and learning curves
- Length of follow-up and losses to follow-up.
- Age
- BMI
- Activity levels after repair. Some studies are in elite sportsmen and women who may put great demands on the repair. Some patients may go back to activity too early.
- Concomitant surgery, or lack of it. For example there was only one concomitant osteotomy in the Moseley series, but some patients had mis-alignment which left uncorrected, increased the failure rate.
- Outcome measures used – re-operation or symptom scores
- Registry requirements/criteria.

The strong adverse relationship between prior attempts at repair and failure mean that most of the older studies will give a misleadingly pessimistic picture if applied to ACI carried out in people with recent onset defects where ACI is the first procedure. Nevertheless, some studies in which ACI was a last-resort salvage procedure reported good results in many patients.

1.3 Results of ACI.

The most useful study is that by from the Stanmore group, by Nawaz and colleagues[23], because this study is the largest, is of good quality, and reports UK practice, albeit from a centre of excellence. The Nawaz paper reports results in 827 patients which allows for very useful subgroup analysis. Mean age at baseline was 34 years, range 14 to 56. Radiographs were taken and assessed for degenerative change according to the Kellgren-Lawrence grading. The ACI procedures were carried out from 1998 to 2008, and all patients were assessed in 2010, allowing a Kaplan-Meier (KM) survival curve to be constructed for over 10 years. 34% (282) of the patients had had previous repair attempts such as microfracture, and they had much poorer graft survival by 10 years – under 25% compared to 75% in those who had had no previous procedures. The recruitment period spanned the generations from ACI-P to ACI-C and on to MACI. There was no difference in survival time between ACI-C/ ACI-P and MACI.

Patients with Kellgren-Lawrence grades 2 and 3 had only 25% graft survival by 10 years. Those with grade 1 fared better initially but by 10 years were catching up on the grades 2 and 3. Those with no degenerative change did much better with about 70% graft survival at 10 years.

In summary, results of ACI are poorer in;

- Patients who have had previous attempts at repair
- Those with early OA as reflected in Kellgren-Lawrence grades 1 to 3.
- Combining these led to very poor results – ACI in a patient with previous repair and K-L grade 3 had little chance of survival at 10 years.

Size of lesion did not affect survival.

1.4 Results of microfracture

The long-term evidence on microfracture was more sparse. We note a comment by Salzmann, and colleagues[35] that;

"*The general body of literature concentrating on the clinical outcome following microfracture at the knee joint is surprisingly light when compared with its clinical popularity".*

This applies particularly to studies reporting outcomes beyond 5 years. There are few of these so we relaxed our exclusion criterion of a minimum of 40 patients in observational studies.

Gobbi[8] in a series of 61 patients followed for 15 years, reported good results at short-term follow-up but that deterioration could be expected after 2-5 years. Their failure rate, defined as need for re-operation, was only 7 patients (11%) but 40% showed osteoarthritic changes.

Gudas et al[36] reported outcomes in the microfracture arm of a trial against mosaicplasty. In 29 patients, 11 (34%) had failed (required re-operation) by 10 years. Most failures occurred by 40 months. Defects averaged 2.8cm^2.

Solheim et al[32] followed up 110 patients for 10 -14 years after microfracture reported failure need for further surgery in 39% and poor results (Lysholm score of 64 or less or needing knee replacement) in 46%. They commented that although outcomes score improved after microfracture, normal knee function was usually not achieved.

Steadman et al[34] reported better results in a series of 72 patients followed for an average of 11 years, range 7 to 17 years. Their average defect size was 2.8cm^2 and mean duration of injury was 3 years (range 9 month to 7 years). Two failures were excluded, as were patients having concomitant surgery, or who had OA, and those over 45 – so the 72 patients are a subset of 302. At year 7, 59 (80%) had

improved by having less pain. Children tend to do well with any intervention, and much better than adults. So the good results may reflect the good prognostic indicators.

By far the largest microfracture study has not yet been reported in full, and unfortunately only provides follow-up data up to 5 years. Layton and colleagues from Quorum Consulting reported results in 3,498 patients using data from an American claims database, published as an abstract from the ISPOR conference[20] but with greater detail available in the poster which is on the Quorum website.[21]

Not all the patients reported are relevant to this report, because they included 351 MediCare patients with average age 73. We excluded them. And even the "commercial" group is older, at mean age 47, than most patients being considered for ACI. However, they do provide a good guide to the success of microfracture in routine care and have impressive numbers. Layton and colleagues[21] reported failure rates (further surgery) of 9% within one year, 18% at 3 years, and 32% by 5 years. Data on analgesic consumption suggests that others did not have further surgery, but needed opiate or other analgesia.

The future of microfracture has been reviewed by Bert[37] who points out that the landmark studies of microfracture, such as by Steadman[34] did not have control groups of debridement alone. Bert cites the 2013 study by Gudas and colleagues[38] as the only trial in which microfracture was compared with debridement alone, and which showed no difference. Unfortunately the Gudas trial was quite small (34 patients per arm), had only 3 years follow-up, and would not score well on the Cochrane risk of bias checklist. Bert argues that debridement alone will give as good results as microfracture but without damaging the underlying bone, which would reduce the likelihood of success with later ACI.

2 Time to failure studies

Caveats. When considering survival curves extrapolated beyond the observed data, it should be borne in mind that the extrapolation assumes that the curve based on the observed data will continue. When using parametric fits for extrapolation (any fit irrespective of the equation that describes it) the usual option is to select what is considered to be the best fit to the observed data. Unfortunately there is no universally applicable method to determine the best fit and opinions may differ. With some data most well-fitting models will produce similar extrapolations, however with ACI data this has not been the case. Selecting several plausible models that produce different extrapolations should bracket what can be argued to be the best estimate of behaviour beyond the observed data.

Some of the results do not have PSA analyses because it was not possible to get a meaningful covariance matrix for some curves because (due to lack of numbers for patients and for events) and the uncertainty was not quantifiable. The only way to get curve parameters was using a digitised KM (rather than reconstructed IPD) with the non-linear regression STATA command specifying candidate parameters. There are uncertainties about the curves and no CI could be put on them (Appendix 5). Probabilistic analysis with "curve uncertainty" was not possible.

Methods

Published Kaplan-Meier (KM) graphs were digitized and individual patient data reconstructed using the Guyot et al method.[39] Where published graphs had the appearance of KM plots but authors did not specify their method it was assumed to be Kaplan-Meier. Where plots were presented as scatter graphs rather than stepped lines it was assumed data points represented the top, rather than bottom or midpoint, of a stepped fall in survival.

Parametric models of time to failure were used to explore failure rate beyond the observed data. In the absence of patient numbers this was done by least squares non-linear regression. Where patient numbers allowed use of the Guyot method[39] to reconstruct IPD the models were implemented in Stata (version 12) with the streg command and or using the stgenreg package of Crowther and Lambert 2013.[40] Standard models (exponential, Weibull, loglogistic, lognormal, Gompertz and gamma) were explored together with additional models for increasing hazard through time, either after an initial phase of decreasing hazard (bath tub model) or with linear increase in hazard (Rayleigh models). Confidence intervals (95%) were estimated with the delta method. The bath tub model was

investigated because it has previously been found useful for modelling failure rates after total hip replacement.[41]

Linearly increasing hazard models were tried because microfracture failure rate during 12 years of follow up of patients with osteoarthritis (Bae et al[42], an excluded study for this report, because patients had OA and were older) was found to be best fit with such models.They were therefore judged worth investigating. Linear hazard models were used with one or two parameters in which survival is described as:

A] $S = \exp(-\lambda * t^2)$

B] $S = \exp(-(\lambda_0 * t + \lambda_1 * t^2))$

($\lambda_0 > 0$; when is λ_0 is zero, S conforms to equation 1)

Model fit was judged using information criteria and by visual inspection of cumulative hazard plots[43] and of KM plots. One study provided Cox multivariate regression analysis of patient subgroups. The hazard ratios from these analyses were used to estimate subgroup failure rates using two methods: 1] Lognormal model hazard was calculated for the baseline subgroup and multiplied by the appropriate HR for each of the other subgroups. The time to failure for these subgroups was estimated from: exp (- cumulative hazard). 2] Weibull or linearly increasing hazard model survival for the subgroups was estimated from: exp (ln (baseline subgroup survival) * HR)).

Lognormal model hazard was calculated from:

Hazard = A/B where:

A = C * D and

C = $\exp(-0.5 * ((\ln(t) - \mu)/\sigma)^2)$ and

D = $(t * \sigma * \sqrt{2} * \sqrt{\pi})^{-1}$

B = $1 - \Phi(\ln(t) - \mu / \sigma)$ where Φ is the standard normal distribution.

Parametric models and KM plots are presented in Appendix 5. The remit for this report was to exclude studies with less than five years of time to event data, therefore except in exceptional circumstances such studies were excluded.

2.1 Description of time to failure data

Seven relevant published studies were identified that presented KM plots extending to at least five years. Estimates of IPD reconstructed from such plots are best served (i.e. likely to be more accurate) when the total number of events, and of patients, are reported and when accompanied by a risk table indicating the number of participants remaining at risk at multiple time intervals, and when the graphical display is of sufficient quality to unambiguously identify the times at which events

occurred. Extrapolation of parametric models fit to such IPD data is more likely to be reliable for more mature data; that is where follow up is sufficient that the number of events has reduced the probability of survival at the end of the plot to a low value. A rough estimate of maturity is whether median survival has been reached.

Some of the included studies aggregated event times to yearly intervals. This may be because precise times of failure were not recorded. The impact of this on subsequent use of data is difficult to gauge. Risk tables were rarely presented, and in some studies reporting subgroup analyses the number of patients as well as the number of events for some subgroups was not reported. Median survival was only reached in one study. One study presented KM analyses in scatter plots rather than a more conventional stepped plot. In this study it was difficult to be certain whether data points represented the top, bottom or midpoint of a step in survival. These characteristics are summarised in Table 1.

Table 1. Time to event data presented in relevant studies

Item/study[℧]	Knutsen et al 2007[19]	Minas et al 2014[44]	Moseley et al 2010[22]	Nawaz et al. 2014 [23]	Niemeyer et al.2014[25]	Vanlauwe et al., 2011[1]
Patient number	Yes	Yes[¥]	Yes	Yes[¥]	Yes	Yes
Event number	Yes	Yes[§]	Yes	Yes[§]	Yes	Yes
Risk table	No	No	No	Yes[∞]	No	Yes *
Events annualised	No	Yes	No	Yes	No	No
Stepped graph	Yes	No	Yes	Yes	Yes	Yes
Median survival	No	No	No	No	No	No

℧ Jungmann et al., 2012[17] presented Kaplan Meier plots for time to end of follow up and of time of failure for those who failed, so as these did not allow analysis of time to failure the study was excluded. ¥ Minas reported patient numbers only for the whole cohort and for previous and no previous intervention subgroups. Nawaz reported patient numbers for whole cohort, for previous and no previous intervention subgroups and for site of intervention subgroups but not for grade of preoperative degenerative change subgroups. § Minas and Nawaz event numbers were only provided for the whole cohort. ∞ a risk table was only available for the whole cohort. * the risk table for the MF group was anomalous.

The definition of treatment failure varied between studies; failure either consisted exclusively of surgical re-intervention or a mixture of surgical re-intervention and a poor functional or pain score relative to pre-treatment. Table 2 summarises the treatment failure definitions used in the relevant studies.

Table 2. Time to failure definitions used in relevant studies

Nawaz 2014[23]	(1) graft delamination proven either by MRI or arthroscopy; (2) a new surgical intervention, including arthroplasty, high tibial osteotomy, or another revision procedure (graft hypertrophy was not counted as a failure); (3) a VAS pain score within ≤ 2 points of the preoperative score; or (4) a Stanmore functional score that was the same or worse than the preoperative score.
Minas 2014[44]	(1) graft failure with revision using partial knee arthroplasty or TKA; (2) graft failure with revision cartilage repair; and (3) graft survival but development of new defects elsewhere in the same knee necessitating additional surgery (progression of disease).
Moseley 2010[22]	Needed an operation after ACI that necessitated removal of the graft, confirmed a loss of defect fill, or violated the subchondral bone (eg, abrasion chondroplasty, microfracture, drilling, unicompartmental knee replacement, total knee replacement).
Vanlauwe 2011[1]	Re--intervention affecting more than 20% of the index lesion. Time to treatment failure was the time between the end of the surgical procedure and "the date of failure or re-intervention".
Knutsen 2007[19]	Failure if the patient needed a reoperation because of symptoms due to a lack of healing of the treated defect. The need for shaving or trimming of a lesion was not defined as a failure.
Niemeyer 2014[25]	Re-intervention surgeries.
Jungmann 2012 [17]	Time to event was defined as time to revision surgery.
ACTIVE trial unpublished	Cessation of treatment benefit in which: "two of the following three conditions below are satisfied: a] Overall knee status judged by the assessor as not improved from pre-operative condition (cessation of benefit form), b] No gain in independently assessed Lysholm knee score compared with pre-operative score, c] No gain in patient's self-assessed Lysholm knee score compared with pre-operative score". Within element a] re-intervention / additional procedures could be judged to be treatment failure.
* Kaplan-Meier ACI survival curves (time to failure) were reported: a] in the "best case" scenario patients lost to follow-up (n = 5 of 58) were assumed to have their graft still intact, and b] in a "worst case" scenario patients lost to follow-up grafts were assumed to have failed immediately on loss to follow-up. There were ten ACI failures that required revision surgery (2 of these also had "poor" Cincinatti scores). § Text taken from the methods section .	

2.2 Results of ACI trials

Four small RCTs, each with two arms were identified. Two (Knutsen et al., 2007[19], N = 80 patients; Vanlauwe et al., 2011[1], N = 112 patients) compared ACI with MF. The RCT of Bentley et al., 2012[11] (N = 100 with about 10 years of follow up) compared ACI versus mosaicplasty – we are interested only in the ACI arm and these patients were included in the larger study of Nawaz et al. [23] and so are not considered further. The RCT of Gudas et al. [36] compared MF with mosaicplasty but did not satisfy inclusion criteria (see appendix 8).

Figure 1 summarises the reconstructed time to failure KM plots for the Knutsen and Vanlauwe RCTs which extended to 5 and 6 years of follow up respectively.

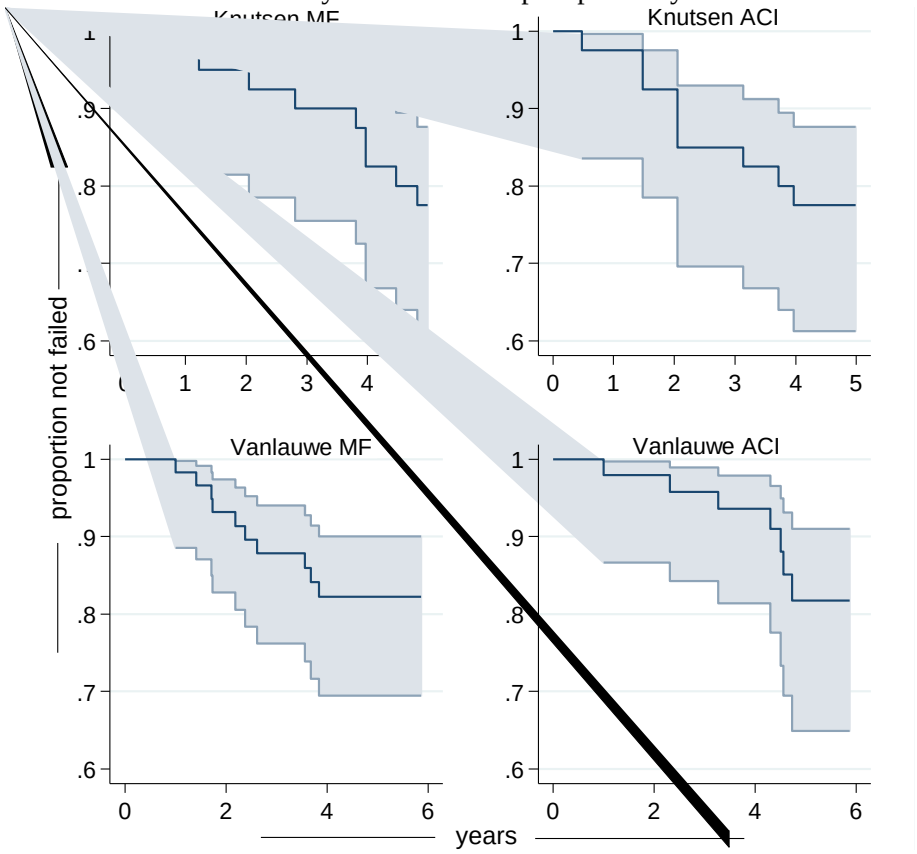


Figure 1. Reconstructed KM plots (95% CI) of time to failure in two RCTs.

In these small studies the observed data is associated with considerable uncertainty. Extrapolation of parametric models was associated with large uncertainty beyond the observed data. Figure 2 illustrates this for Weibull fits extrapolated to 50 years (other models are presented in Appendix 5. The short follow up and small size limits their usefulness for modelling failure rates beyond 5 years. Additional (non RCT) studies of larger size and longer follow up were sought.

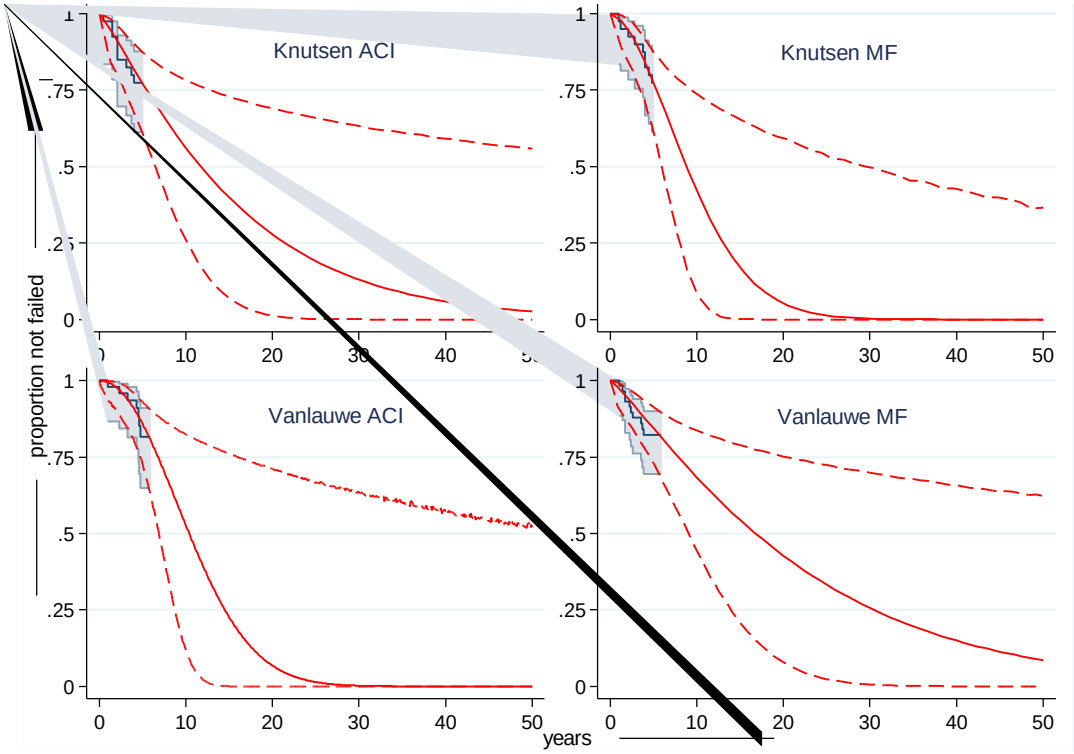


Figure 2 Extrapolated Weibull distributions fit to reconstructed IPD from the RCT studies.

Note: There is some doubt about the reliability of the Vanlauwe MF arm because of an anomaly in the published risk table which coincided with a flattening of the KM plot at 3 years. Saris et al. 2009[45] reported 3 year MF data for this trial.

2.3 Results of ACI observational studies

Four single arm ACI studies with KM plots were included. Niemeyer et al[25] reported event times for 70 German patients with follow up to 5 years; Minas et al[44] and Mosely et al[22] reported time to failure for 210 and 72 US patients respectively with follow up extending up to or beyond 10 years; Nawaz et al,[23] reported annualised time to failure for 827 UK patients with follow up to about 10 years. ACI patients from Bentley et al., 2012[11] and from Biant 2014[14] were encompassed in the study of Nawaz and so survival data from these are not considered separately. For the whole cohort Nawaz reported both annual event and censoring numbers for each year so that the IPD could be reconstructed without resort to the Guyot et al[39] algorithm. Jungmann et al[17] presented time to re-intervention for 413 of 500 patients (selected follow up 2 to 11.8 years) with analysis truncated at 5 years; this KM was not comparable with those in other studies and IPD was not reconstructed.

Patient characteristics in the ACI studies are summarised in Table 3. Typically lesions were full thickness with study mean size ranging from 2.7 to 8.4 cm^2 in patients with mean age 30 to 40 years most of whom had experienced previous interventions. Symptom duration prior to intervention varied between studies.

Table 3 Baseline characteristics reported for patients in six ACI studies

	Bentley[11]	**Biant**[14]	**Knutsen**[19]	**Minas**[44]	**Moseley**[22]	**Nawaz**[23]	**Niemeyer**[25]	**Vanlauwe**[1]
N	100§**	104**	40	210	72	827	70	51
Follow up φ	>10 [10-12]	[10-12]	NR$	>10	10	6.2 [2-12]*	10.9 SD 1.1	NR
Age φ	31.3 [16-49]	30.2 [15-49]	33.3 [NR]	35.8 [8-57]	37.0 SD 9.27	34 [14-56]*	33.3 SD 10.2	33.9 SD 8.5
Male (%)	58§	52.9	60	53.8	61	59.6	35.7	61
Defect size (cm^2)*	4 [1-10.5]	4.8 [1.2-25]	5.1 [NR]	8.4 SD 5.5	5.2 [0.4-23.5]	4.09 [0.64-20.7]	6.5 SD 4.0	2.7 [1-5]
Previous (%)	94	70 €	93	42	74	34	62.8	88
Mean no: previous	1.5	1.3 [0-5]	1.6	NR	NR	NR	NR	NR
Weight (kg) *BMI kg/m^2*	NR	NR	81 [NR]	*26.7 SD 4.6*	*27.2*	NR	NR	78.3 SD 13.9
Symptom duration φ	7.2* [0.75-20]	7.8*	3Φ	NR	NR§§	NR	Several	1.97Φ [0-18]
Defect site ¥				NR				
MF	53.0	44.0	89.0		72#	51	41.1	100
LF	18.0	16.0	11.0		18	13	18.6	
Pa	25.0	35.0	0		NR	24.0	20	0
Tr	3.0	5.0	0		10	6.0	2.9	0
Mult	0	0	0		NR	6.0	17.1	0

Φ = years; * = mean ; Φ = median; [ ] = range ; no: = number; SD = standard deviation; $ results reported for 5 year follow up. ** consecutive patients; € = excludes debridement; § ACI + mosaicplasty groups. ¥ = %; # 17% of patients in Moseley et al., had multiple sites; §§ 65% had acute onset; NR = not reported; MF = medial femoral; LF = lateral femoral; Pa = patellar; Tr = trochlea; Mult = multiple. Note: six of 57 patients in Vanlauwe did not get treated

Figure 3 (upper) shows the reconstructed KM failure plots for the four single arm and two RCT ACI studies that provide relevant data to at least 5 years. It should be appreciated that definitions of failure were not identical between different studies and the mix of patients that had or had not experienced previous intervention also differed between studies. Because of study size the uncertainty in the Nawaz[23] data is less than that in the other studies. Up to about 6 years there is reasonable consonance for most studies, thereafter the prognosis appears worse for Nawaz patients,

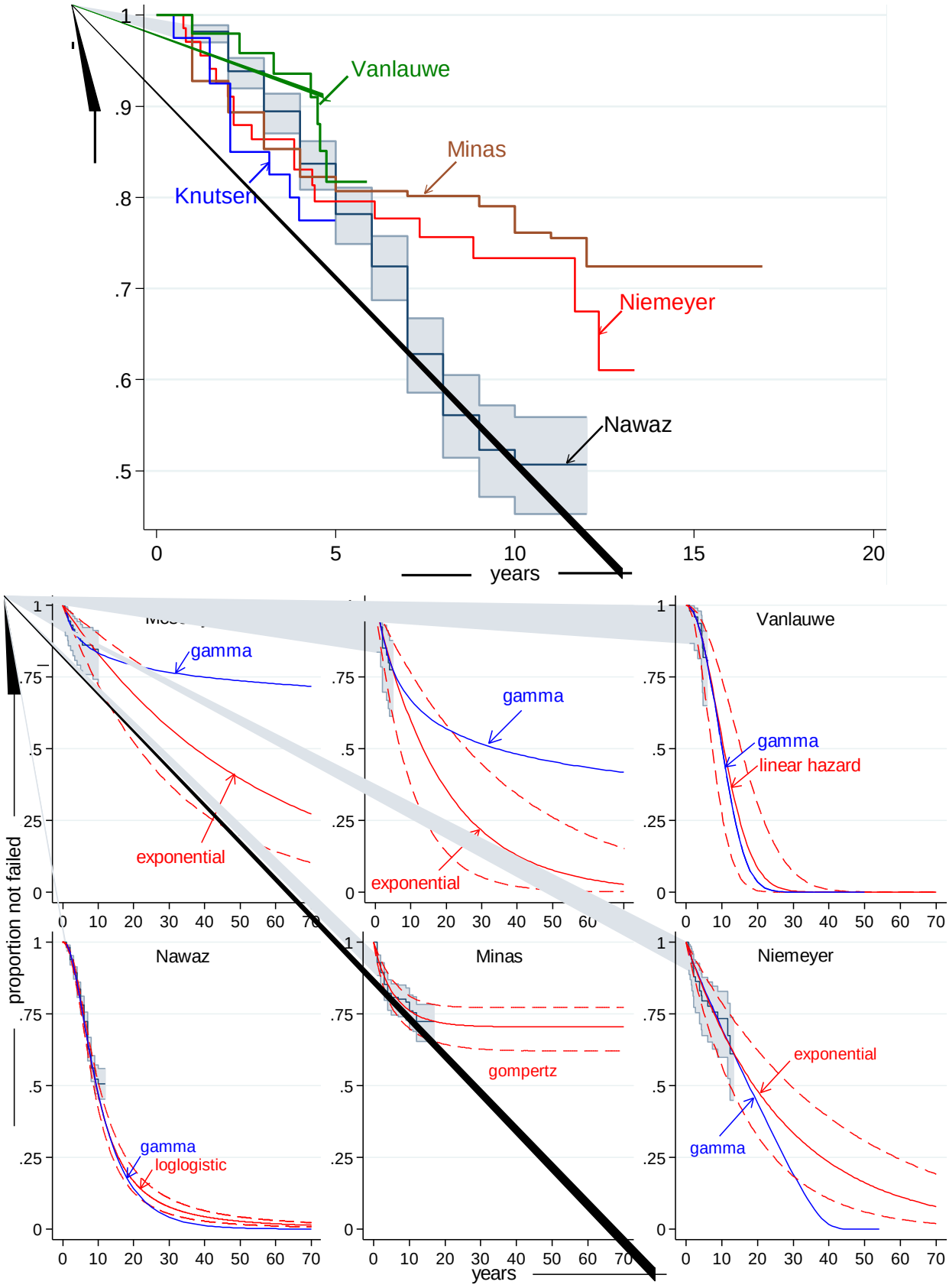


Figure 3 Upper: Reconstructed Kaplan-Meier plots for ACI studies. Lower: best parametric fit (95% CIs) and gamma models for six ACI arms

(Note: a gamma model could not be computed for Minas).

but this appears partly due to flat portions of the KM curves for the other studies where patients at risk have diminished considerably and uncertainty is at its maximum. These data indicate that the Nawaz study is unlikely to flatter failure rates after ACI and that to about six years of follow up the Nawaz study is reasonably consistent with other studies; beyond 6 years the KM analyses of the other studies are likely to be less reliable because of smaller study size. Combination of these different studies would be difficult to justify because of clinical heterogeneity.

Figure 3 (lower) shows parametric models for these studies extrapolated to 70 years. Gamma fits illustrate differences seen between studies when applying the same single distribution to all, also shown are best fits for each study. Judged according to information criteria, various parametric models provided best fits: Knutsen exponential, Minas Gompertz, Moseley exponential, Nawaz loglogistic, Niemeyer exponential, andVanlauwe linear hazard. For Nawaz and Vanlauwe the best fits differed very little from the gamma model. The best fit models for Knutsen, Nawaz, Niemeyer, and Vanlauwe studies predict more than half ACI interventions fail within about 30 years, whereas the Gompertz model based Minas indicates about half or more ACIs remain without failure up to 70 years, and the gamma model for Moseley predicts about 25% remain without failure to 70 years.

Potential reasons for differences in KM plots and best fit models between these studies are manifold; they include uncertainty in the observed data resulting from small numbers of participants and in some studies short term follow up, different reliability of IPD reconstructions, and differences in study populations particularly with regard to experience of previous intervention(s), the degree of degenerative change, and location and size of lesion.

Post-failure treatments

Biant reported the revision surgeries following ACI failure as: 44.4% TKR or unicondylar knee replacement or patellofemoral joint replacement or medial and patella-femoral knee replacement; 25.9% ACI; 18.5% high tibial osteotomy; and 11.1% arthrodesis or chondroplasty. In Minas 19/53 patients with failed grafts went on to knee arthroplasty within the follow up period, 27/53 had revision cartilage repair procedures, and 7/53 refused further treatment after failure.

Studies with patient subgroup analyses

Jungmann et al[17] and Bentley et al[11] reported data (but not KM plots) comparing failure rates between subgroups of patients. Jungmann[17] provided evidence that increased revision was associated with previous intervention, previous bone marrow stimulation, female gender, and ACP-P relative to other ACI types. Bentley provided 5 year revision rates by subgroup; only older age appeared associated with increased probability of revision (note these patients were included in the Nawaz study).

Both Minas and Nawaz studies presented KM plots for subgroups of patients but neither reported event numbers by subgroup and patient numbers were only available for some subgroups of patients. Nawaz provided Cox regression hazard ratios for several subgroups of patients. Because of its size, length of follow up, the use of multiple surgeons, and inclusion of UK patients, the Nawaz study was judged to be the most relevant ACI study for the current decision problem. Therefore the focus in this section is on the Nawaz study and the results from Minas are presented for comparison.

2.4 Nawaz et al 2014 study of UK patients

The most useful study is by Nawaz and colleagues.[23] For the whole Nawaz cohort (N=827) a loglogistic distribution provided the best fitting parametric model. Figure 4 shows the reconstructed KM plot together with the loglogistic model extrapolated to 50 years; the model predicts that after about 30 years approximately 90% of patients would have failed. The partition of failures according to elements of failure definition (Table 2) was not reported (e.g. the proportion of failures receiving previous intervention at the time of failure is unknown).

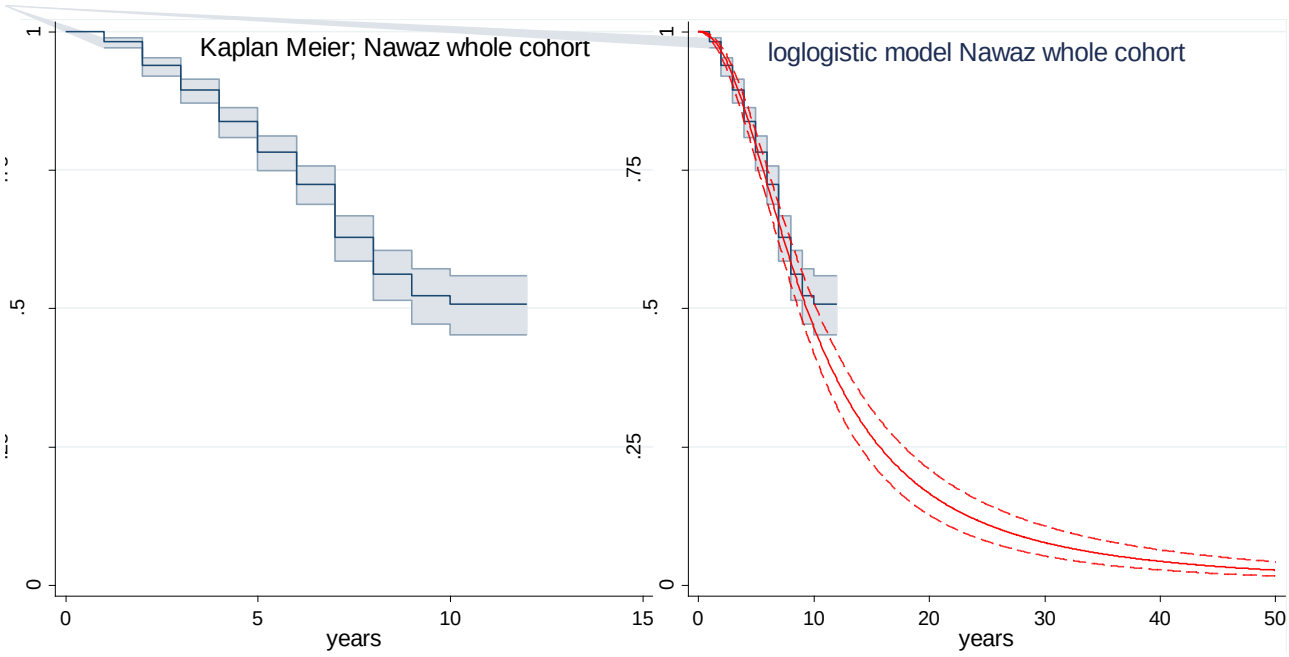


Figure 4 Reconstructed Kaplan Meier plot and extrapolated loglogistic model for the Nawaz whole cohort.

2.4.1 Patient subgroups examined in the Nawaz study

Nawaz et al.,[23] presented Kaplan Meier plots for subgroups of patients categorised according to: (i) receipt of a previous intervention; (ii) site of intervention; (iii) grade of degenerative change; and (iv) type of intervention received (MACI or ACI). The authors used univariate and multivariate Cox

regression to investigate if these and also if age and size of defect were influential for failure. The most influential patient covariate was previous intervention ($p < 0.001$; multivariate HR versus no previous intervention: 4.72, 95% CI: 3.5 – 6.4). Grade of degenerative change ($p < 0.001$), site of intervention ($p = 0.036$ for best versus worst site), and age at operation ($p < 0.001$) were also significantly influential whereas type of intervention (ACI or MACI) and lesion size were not ($p = 0.860$ and $p=1.00$ respectively). The authors did not report on a test of the proportional hazards assumption. The AG reconstructed the subgroup KM plots and used reconstructed IPD to investigate good parametric models for the data. Additionally AG investigated the effect of adjusting parametric models using the multivariate hazard ratios reported by Nawaz et al.

Previous and no previous intervention

According to information criteria lognormal and gamma distributions provided good models for patients who had previous or had no previous intervention (debridement was not included as a previous intervention). When the HR reported by Nawaz[23] (previous versus no previous intervention) was applied to either lognormal or Weibull models the resulting model was very similar to that fit to the previous subgroup IPD (Figure 5). These results indicate that there was likely to be little difference between the subgroups in the distribution of other covariates influential for failure.

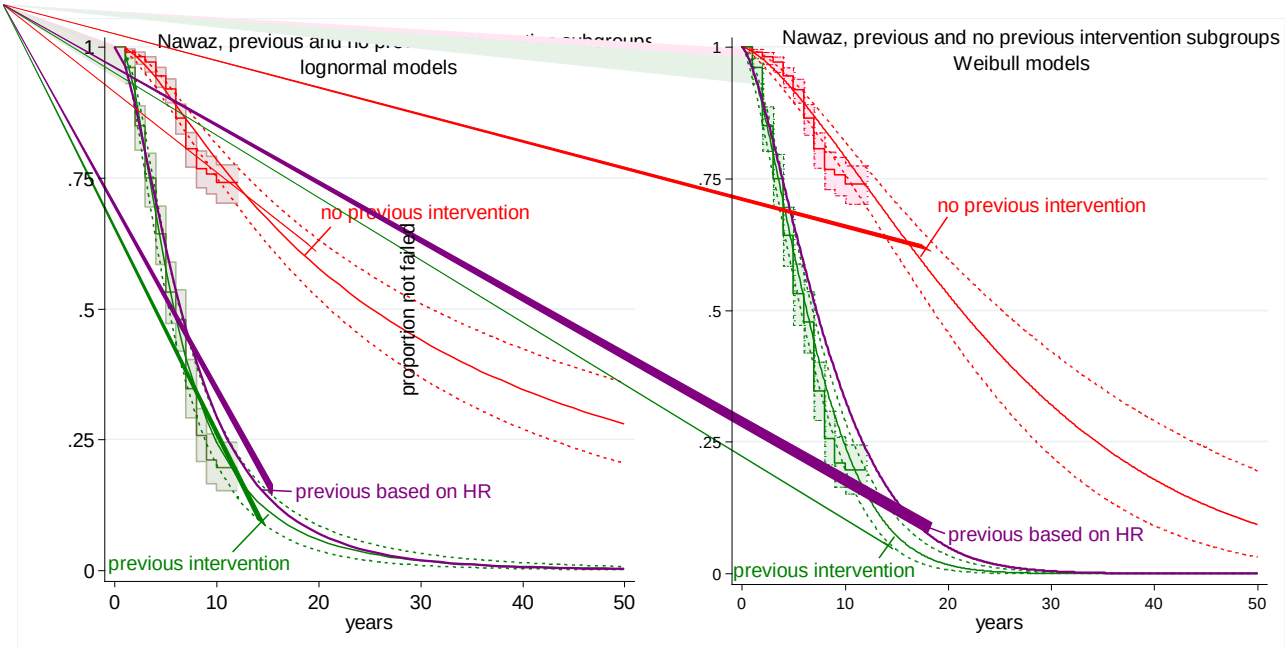


Figure 5 Reconstructed KM plots (95% CI) and extrapolated lognormal (left) and Weibull (right) parametric models for Nawaz et al., 2014 patients according to previous intervention or no previous intervention.
Dashed lines are 95% CIs.

Site of intervention

Nawaz[23] published KM plots and multivariate Cox regression hazard ratios comparing time to failure for five subgroups that differed according to intervention site (medial femoral, n=421; lateral femoral, n=109: patella, n=200; trochlea, n=50; multiple sites, n=47) . Hazard ratios versus the lateral femoral condyle group as baseline reference were: medial femoral condyle 1.806 (95% CI: 1.036 – 3.149, p = 0.037): patella 1.323 (95% CI: 0.745 – 2.351, p = 0.339) ; trochlea 1.409 (95% CI: 0.625 – 3.174, p = 0.0408), and multisite 1.678 (95% CI: 0.731 – 3.851, p = 0.222). Reconstructed KM plots were similar for all but the lateral condyle group which exhibited the least failure. Lognormal distributions provided the best fit parametric models to reconstructed subgroup IPD. Figure 6 shows reconstructed KM pots and hazard ratio-adjusted lognormal models. Applying the reported hazard ratios diminished the apparent superiority of the lateral femoral condyle subgroup seen in the Kaplan Meier plots and indicated that relative to other subgroups the lateral femoral population may possibly have been favourably free of detrimental covariates for failure (e.g. previous treatment and high grade degenerative change). Similar results were obtained with Weibull models.

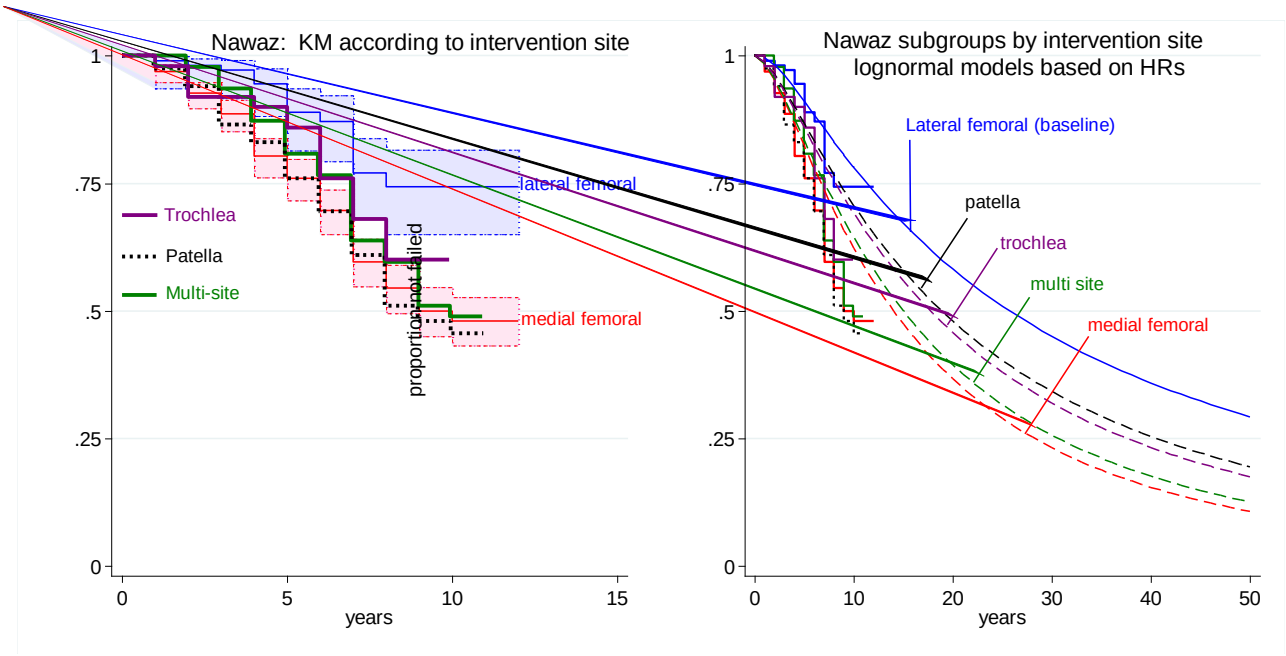


Figure 6 Reconstructed KM plots and lognormal models for time to failure according to site of intervention.
For clarity KM 95% CIs are only shown for lateral and medial femoral condyle sites and have been omitted for the model fits.

Grade of preoperative degenerative change

Nawaz[23] published KM plots and multivariate Cox regression hazard ratios comparing time to failure for four subgroups categorised according to grade of degenerative change (Kellgren-Lawrence

grades). Hazard ratios versus the grade 0 subgroup as baseline reference were: grade 1, 1.542 (95% CI: 0.930 – 2.557, p = 0.093); grade 2, 1.869 (95% CI: 1.381 – 2.529, p = <0.001); grade 3, 1.985 (95% CI: 1.092 – 3.610, p = 0.025). Patient numbers were not reported and parametric models were fit to digitised KM plots using non-linear regression. For different subgroup grades lognormal and linearly increasing hazard models produced acceptable fit to digitised KM plots in Appendix 5. When the HRs reported by Nawaz were applied to either of these models the resulting plots for different grades were more similar to each other than was apparent from KM plots or fits to KM plots Figure 7. These results may indicate that some of the superiority of the grade 0 subgroup apparent in the KM plots was possibly due to relative freedom of this group from covariates that tend to increase the probability of failure.

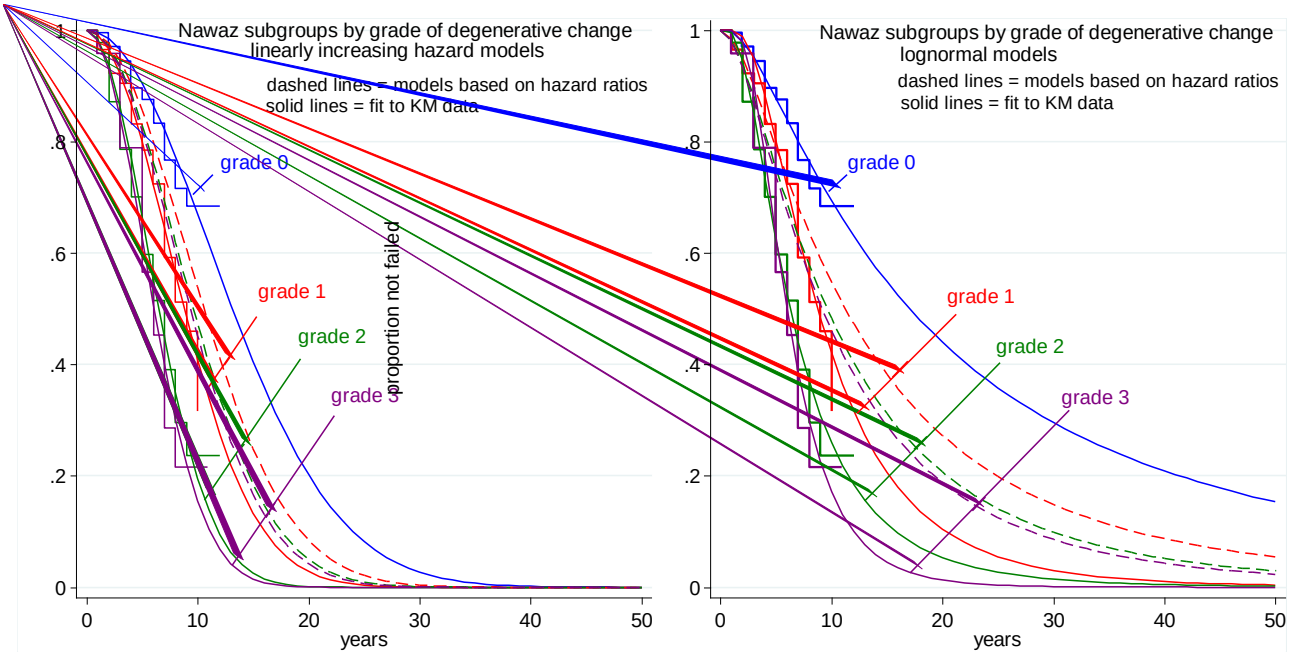


Figure 7 Reconstructed KM plots linearly increasing hazard and lognormal models for time to failure according to grade of degenerative change.
Solid lines are model fit to KM data, dashed lines are models adjusted by application of hazard ratios.

2.5 Minas et al 2014 study

Minas et al[44] performed several KM analyses for various subgroups of patients. Patient numbers were only reported for the comparison of previous intervention versus no previous intervention groups. Like Nawaz [23], worse failure rates were found for patients who had experienced previous intervention. As was seen for the whole Minas[44] cohort, the subgroup failure rates flattened after about 6 years and extended to as far as 17 years with relatively few failure events. Thus failures were much less frequent in both Minas subgroups than in the corresponding Nawaz subgroups. No regression analysis was performed in Minas and no hazard ratios were reported. Gamma distributions provided good fits for

both studies' subgroups. Reconstructed KM plots and gamma models fit to IPD for subgroups from both Nawaz and Minas are shown in Figure 8 .

Minas also provided plots for failure according to subgroups that experienced different types of previous intervention. Patient numbers were microfracture N = 13, abrasion arthroplasty N = 30, drilling N = 46. Failure was more frequent after MF than after the other forms of marrow stimulation (Appendix 6). (See Discussion on this point.) Concurrent osteotomy resulted in fewer failures.

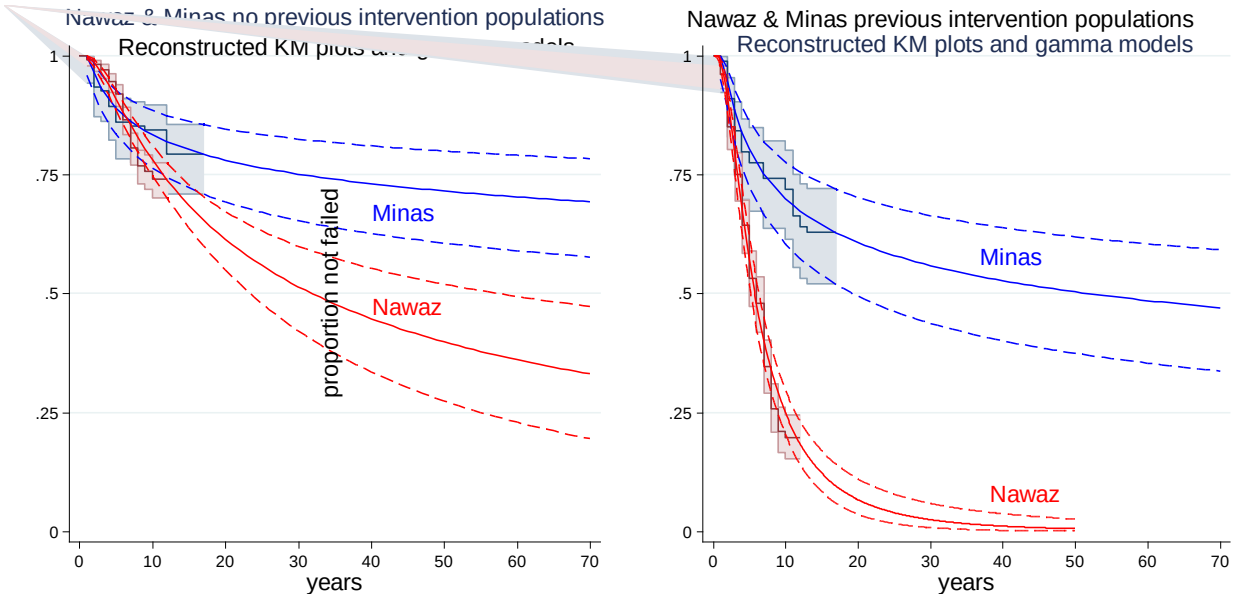


Figure 8 Time to failure for previous intervention and no previous intervention patient subgroups (Minas and Nawaz) showing reconstructed KM plots and gamma models of time to failure.

2.6 Studies of failure after MF (Layton 2015; Knutsen 2007; Saris 2009)

Vanlauwe et al[1] (year 3 results in Saris[46]), and Knutsen et al[19] provided MF failure data to five years. A large US study (Layton et al[20]) which examined records for 3,498 US recipients of MF reported the percentages of failures for patients followed to 1, 3 and 5 years. All patients were followed up to three years. The proportion followed to 5 years was not reported. Layton et al[20]stated "*Failure rates (TKR, Microfracture or ACI) increased with increasing years of follow-up: 9% within 1 year, 18% within 3 years, and 32% within 5 years*". In Knutsen 2007[19], Saris 2009[46] and Layton 2015[20] failure was defined as re-intervention. Only Layton provided information on the type of re-intervention received, as follows: TKR accounted for most re-interventions, 56%, 62% and 66% of re-interventions at years 1, 3 and 5 respectively; MF and ACI accounted for nearly all the remaining re-interventions (very few re-interventions were OATS). The mean age of patients in the Layton study was 47 years (SD 11.4

years), meaning that many would be of an age where TKR would be considered, and there were equal numbers by gender. Table 4 summarises the main characteristics of patients in the MF arms of Knutsen and Saris.

Table 4 Patient characteristics in the microfracture arms of the Saris and Knutsen RCTs

	Knutsen[19]	Saris[46]
N	40	61
Follow up, years	5	5
Mean (SD) age, years	31.1 (NR)	33.9 (8.6)
Male (%)	NR	67
Mean (SD) defect size (cm^2)	4.5 (NR)	2.4 (1.2)
Mean (SD) weight (kg)	82.1 (NR)	80.6 (13.3)
Mean number previous operations	1.4	NR
Previous operation	93%	77%
Median symptom duration, years	3	1.57 [range 0-18]
Site MF	89%	NR
Site LF	11%	NR

Since all patients in Layton were followed up for 3 years, it was possible to reconstruct IPD for an annualised KM plot (assuming failure took place at one and three years and at three years all non-failed patients were censored). Under the assumption that those followed up for 5 years were representative of all those that could have been followed (censoring those without failure at five years) the five year IPD was also estimated. The best fit models (Figure 9) for these were provided by Gompertz distributions and the second best by a gamma model (Appendix 5)

The linearly increasing hazard model provided the best fit for the MF arm of the Knutsen et al[19]. The published 5 year KM plot for the MF arm of the Vanlauwe et al[1] study had anomalous risk table data and interpretation of the KM plot was problematical (Appendix 7), therefore the Saris et al[46] three year KM plot for this study was examined. The best fit was again provided by the linearly increasing hazard model. These and models for Layton et al are summarised in Figure 9. The poorer performance in Layton et al may be attributable to older mean age and or real world performance of MF relative to that for patients carefully selected for an RCT.

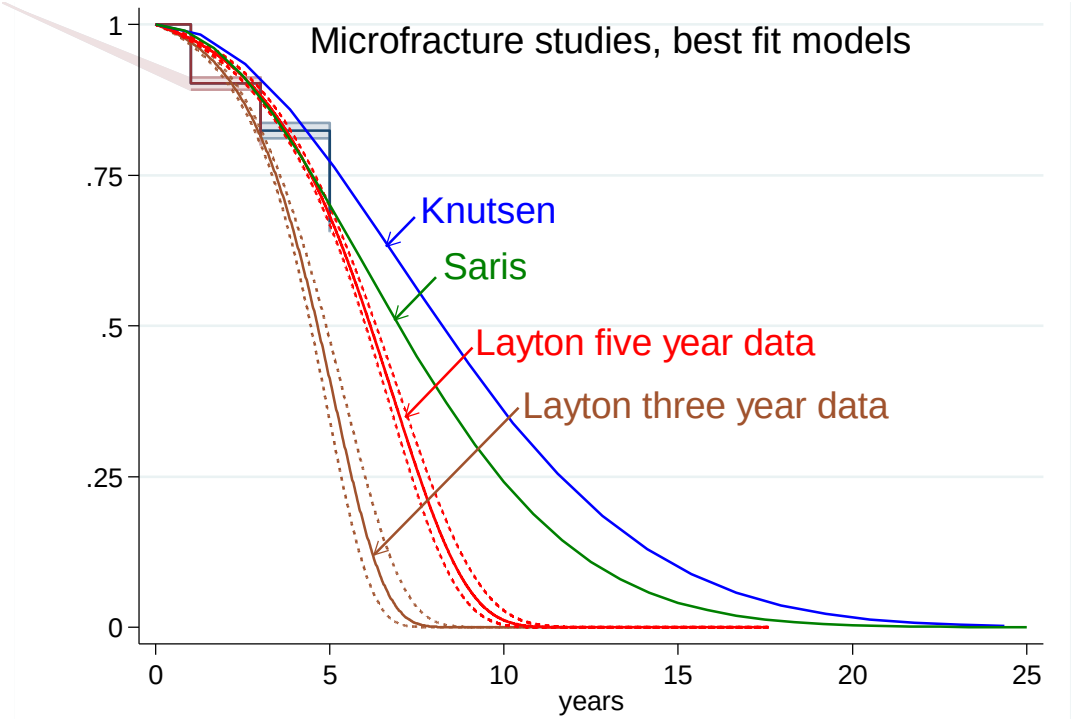


Figure 9 Best fit models to observed MF failure in three studies.

2.7 Comparison of failure after ACI and MF.

A comparison of long-term failure of MF and ACI is problematical in view of the paucity and heterogeneity of studies. AG considered the most reliable comparison may be between the largest UK extended follow up study (Nawaz et al[23]) and the available MF data (described above); a caveat being that failure definitions differed between the Nawaz study and the three available MF studies. When

whole cohorts were compared ACI appears superior to MF (Figure 10).

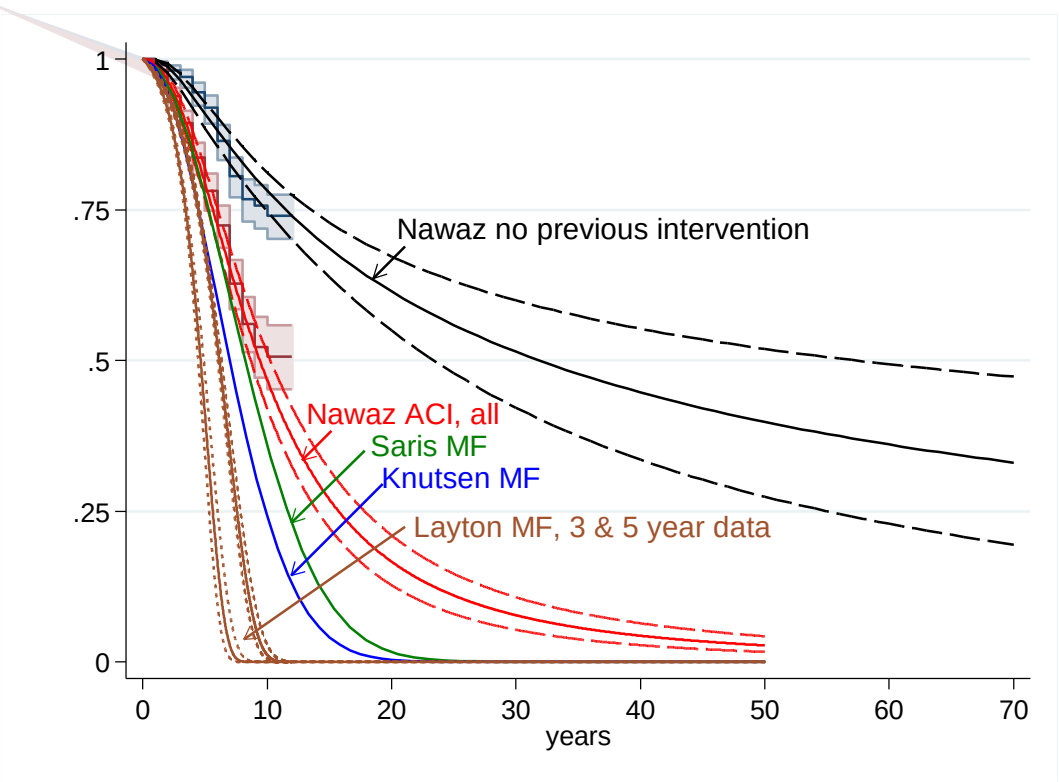


Figure 10 Modelled failure profiles following ACI or MF. Best fit models: for Nawaz whole cohort (all) loglog; for Nawaz no previous subgroup gamma; for Knutsen and Saris MF arms linearly increasing hazard; for Layton Gompertz; (for clarity not all 95% CIs are shown).

No subgroup data was available from the MF studies. Vanlauwe et al[1] did not provide KM plots for subgroups but reported the failure numbers according to whether previous intervention had been experienced (Table 5). Numbers of patients at risk and the number of events were small and the time of events in compared groups was not provided so that firm conclusions are impossible, however these data are suggestive of little effect of previous intervention on risk of failure after either ACI or MF. Salzmann et al[29] followed 454 recipients of MF and compared patient characteristics between those patients that required re-intervention during follow up with those that did not require re-intervention. The former patients on average had received more pre-MF interventions (1.9 ± 2.1 previous interventions) than the latter (1.2 ± 2.1 previous interventions) but the spread in number of preinterventions was great in both cases. Unfortunately, no Kaplan Meier time to event analyses were reported for the no-previous intervention and previous intervention subgroups.

Table 5 Failure of ACI and MFI according to previous intervention (data from Vanlauwe 2011)

	ACI failures/group (risk of failure)	**MF failures/group (risk of failure)**
PREVIOUS knee surgery	6/50 (0.120)	8/47 (0.170)
No Previous knee surgeries	1/7 (0.143)	2/14 (0.143)

1 Previous knee surgery	*3/29 (0.103)*	*4/34 (0.118)*
≥ 2 Previous knee surgeries	*3/21 (0.143)*	*4/13 (0.308)*

In the absence of subgroup KM data for MF the worst performing subgroups investigated by Nawaz were compared with the three MF studies. Lognormal models based on the multivariate hazard ratios reported by Nawaz[23] were used for the comparison (Figure 11).

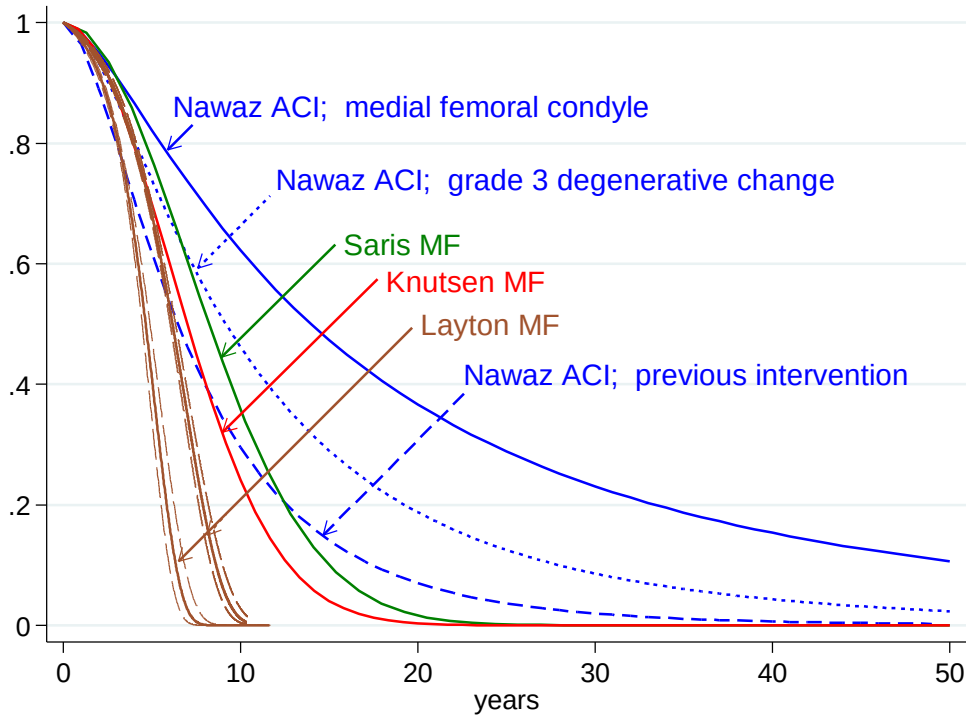


Figure 11 Modelled failure in MF studies compared to worst performing subgroups from Nawaz ACI study

Except for the previous intervention ACI subgroup, the ACI subgroups clearly exhibited less failure than MF cohorts. Lack of data does not allow a comparison with previously treated MF patients. It should be emphasised that uncertainty in these comparisons is substantial especially with regard to the Knutsen[19] and Saris[46] MF arms. Appendix 8 provides analysis of the MF arm of the RCT of Gudas et al[36] excluded on the basis of its small size; the best fit for the reconstructed IPD was a lognormal model which predicted poorer survival than the models for MF for Layton[20], Knutsen[19] and Saris.[46]

2.8 Unpublished ACTIVE trial data.

This multicentre RCT compared ACI (OsCell) versus any of several treatments representing "standard treatment" (depending on surgeon's preference for debridement, or abrasion, or drilling, or microfracture, or mosaicplasty). Kaplan Meier plots for time to treatment failure were submitted for

each trial arm. The trial population had nearly all experienced previous intervention. The best parametric fit for reconstructed ACTIVE trial ACI data was provided by the bath tub model (Appendix 9). This model and the reconstructed KM plot are shown in Figure 12.

Figure 12 Reconstructed KM plots and parametric models for ACI treated populations that had experienced previous intervention (ACTIVE RCT and Nawaz "previous" subgroup).

A gamma distribution provided the best fit to reconstruct IPD for the standard treatment arm of ACTIVE. In Appendix 9 the reconstructed KM and gamma fit for this arm of the trial are compared with available MF for Knutsen, Saris and Layton studies.

2.9 Summary of longer term time to event evidence of treatment failure after ACI and MF

- More long term evidence was available for ACI than for MF.
- Treatment failure definitions differed between studies with varying and sometimes unclear relative contributions to overall failure from re-intervention and from inadequate pain/function scores.
- Study data were generallystill too short-term. Only one published study allowed an estimate of observed median time to failure.
- Most participants in most study populations had experienced intervention(s) prior to enrolment. Where evidence was reported it appears many types of pre-intervention had been tried.
- Two ACI studies with KM analyses extending to at least 10 years reported that treatment failure was far more frequent in patients who had experienced prior-intervention(s); one of these documented greater failure rates after MF than after other marrow stimulation (but patient numbers were small).
- There was no clear time to event evidence that prior intervention influenced failure after MF, other available evidence was meagre.
- Immaturity of failure data necessitated parametric modelling beyond observed data so as to predict life-time failure.
- According to information criteria and visual goodness of fit the best fits of long term failure after ACI were usually characterised by models that when extrapolated beyond the observed data indicated gradually decreasing hazard (probability of failure decreasing with time).
- Conversely good fits to limited data available for MF were characterised by models that indicated linearly increasing hazard (probability of failure increasing with time).
- A single large US study of MF in patients with mean age 47 years indicated that, in this population, TKR was the most frequent intervention after failure of MF.

2.10 Pooling time to failure studies

The second submission from Sobi used parametric models based on pooled data from ACI studies to derive time to failure for ACI. Sobi did not pool microfracture studies. A commentary on the SOBI submission follows in Chapter 4.

The ACI studies pooled by Sobi encompassed studies employing different definitions of failure and recruiting different proportions of previously treated and previousy untreated patients. More judicious pooling can be undertaken in which there is less heterogeneity amongst pooled studies. Therefore, as a supplement to the analysis of single studies described above, the AG have briefly explored pooling of studies for ACI and for MF.

ACI studies.

In the ACI arms of Moseley et al[22], Vanlauwe et al[1], Knutsen et al [19], and Niemeyer et al [25] failure was defined as reintervention and each study included more than 60% of patients that had experienced previous intervention (range 63% to 90%). A lognormal model provided the best fit for these pooled studies (Figure 13).

MF studies

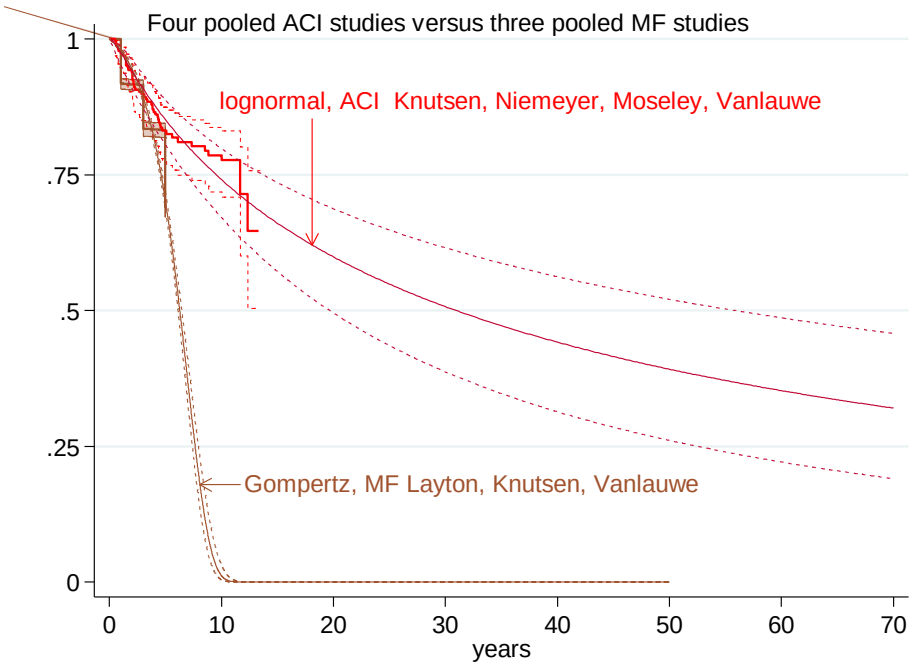


Figure 13 Time to failure after pooling four ACI and three MF studies

In the 3 studies providing MF data failure was defined as reintervention and two predominantly recruited patients who had experienced previous interventions. This was not reported by Layton et al., 2015. When the three studies (Layton et al[20], Vanlauwe et al[1], Knutsen et al[19]) were pooled the resulting KM plot and best fit model (Gompertz) were dominated by the large Layton study (Figure 13). Compared to the pooled ACI studies, failure was more frequent in the MF studies.

The pooled MF studies were dominated by the Layton study. Pooled MF studies excluding Layton et al[20] (i.e. Knutsen et al[19] and Saris et al[46] three year data for the TIG/ACI/01 study) again indicated less failure forACI patients than for MF patients (Figure 14)

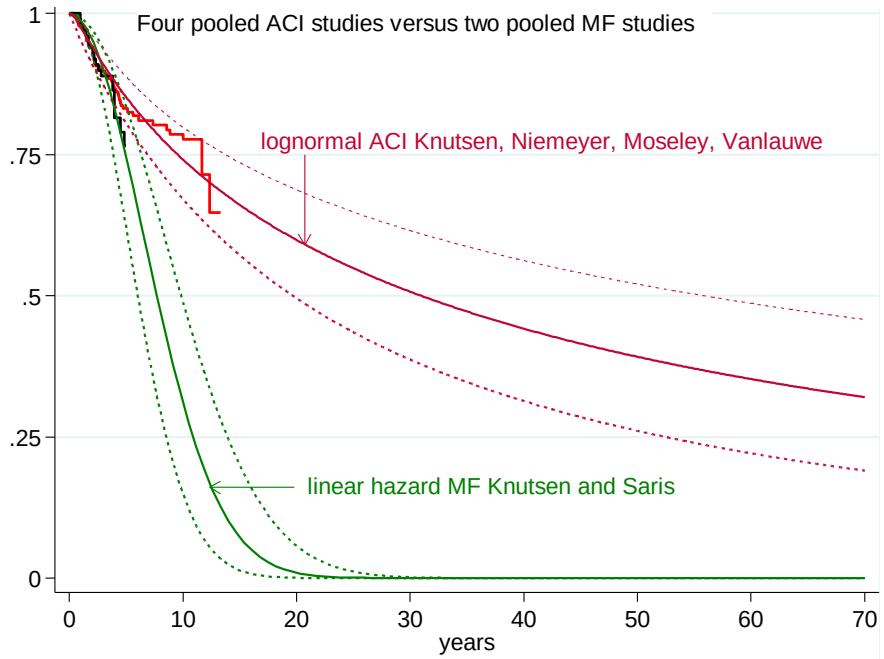


Figure 14 Time to failure after pooling four ACI and two MF studies (Knutsen & Saris)

When the MF arms of Knutsen[19] and Vanlauwe[1] (five year MF data of the TIG/ACI/01 study) were pooled, it was difficult to determine the best fit model using information criteria (Table 6). Only the gamma model of MF failure was superior to ACI (Figure 15). It should be noted that anomalies in the published Vanlauwe MF arm required speculative interpolation of risk table data prior to pooling.

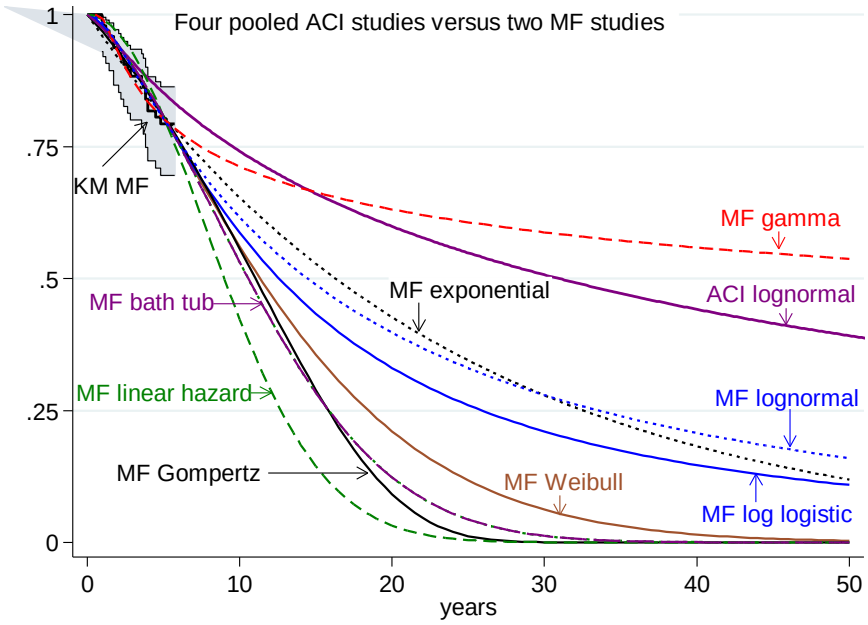


Figure 15 Time to failure after pooling four ACI and two MF studies (Knutsen and Vanlauwe)

Table 6 Information citeria for models to pooled microfracture data from Knutsen and Vanlauwe

Model	Obs	ll(model)	df	AIC	BIC	AIC rank	BIC rank
gamma	101	-58.4314	3	122.8628	130.7081	1	5
exponential	101	-61.9545	1	125.9089	128.524	5	1
weibull	101	-60.7536	2	125.5071	130.7374	4	6
gompertz	101	-61.6625	2	127.325	132.5553	8	8
lognormal	101	-59.7245	2	123.449	128.6793	2	2
loglogistic	101	-60.5069	2	125.0139	130.2441	3	4
linear hazard, 1 parameter	101	-62.1378	1	126.2756	128.8907	6	3
bath tub	101	-61.4594	3	128.9189	136.7642	9	9
linear hazard, 2 parameter	101	-61.4594	2	126.9189	132.1491	7	7

3 Economic analysis

Reported below are the results of the additional economic analyses undertaken, incorporating new parameter values, in particular the survival curves for failure rates reported in Chapter 2. Unless specified, the model structure and parameter values remain the same as those in the initial report.

The different sequences of procedures were ranked in order of increasing cost. We eliminated any categories for which another category was cheaper and more effective (simple dominance). If the incremental cost-effectiveness ratio for a given category is higher than that of the next, more effective alternative this category was eliminated (extended dominance). For the remaining options, we reported the incremental cost-effectiveness ratios (ICERs), measured as cost per QALY gained.

When QALY differences are small, the probabilistic ICERs will fluctuate quite a lot. The deterministic ICERs are more reliable.

3.1 New base case

Data used for ACI failure rates: Nawaz (whole cohort)
Data used for MF failure rates: Pooled data (Layton[20], Knutsen[19], Saris[46])
Cost of harvesting: £870
Cost of implantation: £2,396, as requested by NICE. This includes an inpatient stay. ACI can be done on a day case basis, though it should be noted that because it is often provided as a specialist "regional" service, overnight stays may be unavoidable because of distance. The clinical authors of this report vary between one-night stays for all and some being done as day case. The operation is often open and such exposure is much more painful than the arthroscopic surgery used for harvesting the initial tissue). However mini-arthrotomy may be used.
Microfracture is nearly always a day case procedure.

Table 7 Base-case deterministic and probabilistic cost-effectiveness results

Procedure	Total mean costs £	Total mean QALYs	Incremental costs £	Incremental QALYs	ICER versus MF(ACI)	Comparator
Deterministic - undiscounted						
MF (ACI)	7,736	34.2885	-	-	-	-
ACI (MF)	22,661	35.5596	14,926	1.2711	Extended dominated	MF(ACI)
ACI (ACI)	24,134	35.6999	1,473	0.1403	11,619	MF(ACI)
Deterministic – discounted						
MF (ACI)	6,248	17.1350	-	-	-	-
ACI (MF)	21,400	17.9304	15,152	0.7954	Extended dominated	MF(ACI)
ACI (ACI)	22,461	17.9953	1,062	0.0650	18,844	MF(ACI)
Probabilistic – discounted						

MF (ACI)	6,261	17.1523	-	-	-	-
ACI (MF)	21,410	17.9048	15,210	0.7525	Extended dominated	MF(ACI)
ACI (ACI)	22,532	17.9872	1,061	0.0824	19,487	MF(ACI)

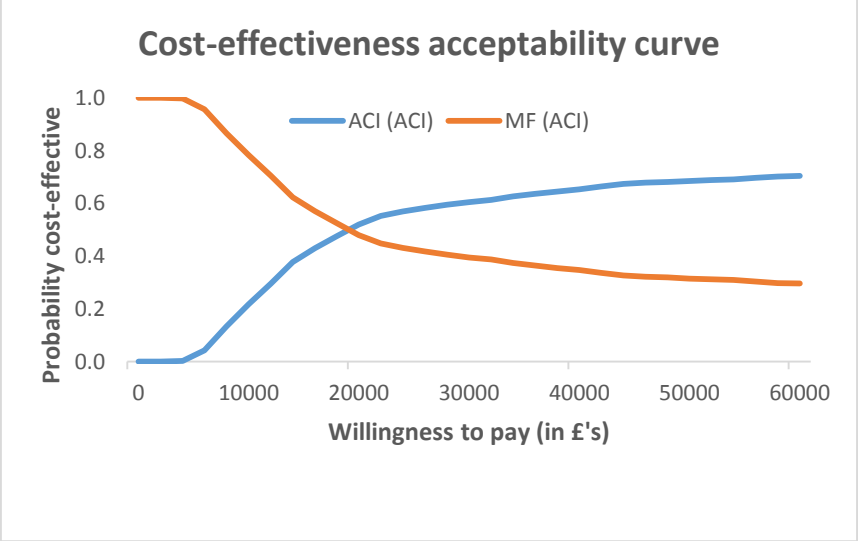


Figure 16 Cost-effectiveness acceptability curve (base-case)

3.2 Sensitivity analyses (Price)

3.2.1 PAS price

Data used for ACI failure rates: Nawaz[23](whole cohort)

Data used for MF failure rates: Pooled data (Layton[20], Knutsen[19], Saris[46])

Cost of harvesting: £870

Cost of implantation: £2,396

Cost of cells: [redacted] (PAS price)

Table 8 Deterministic and probabilistic cost-effectiveness results (PAS price)

Procedure	Total mean costs £	Total mean QALYs	Incremental costs £	Incremental QALYs	ICER versus MF(ACI)	Comparator
Deterministic - undiscounted						
MF (ACI)	[redacted]	34.2885	-	-	-	-
ACI (MF)	[redacted]	35.5596	[redacted]	1.2711	Extended dominated	MF(ACI)
ACI (ACI)	[redacted]	35.6999	[redacted]	0.1403	[redacted]	MF(ACI)
Deterministic – discounted						
MF (ACI)	[redacted]	17.1350	-	-	-	-
ACI (MF)	[redacted]	17.9304	[redacted]	0.7954	Extended dominated	MF(ACI)
ACI (ACI)	[redacted]	17.9953	[redacted]	0.0650	[redacted]	MF(ACI)
Probabilistic – discounted						
MF (ACI)	[redacted]	17.1633	-	-	-	-
ACI (MF)	[redacted]	17.9109	[redacted]	0.7477	Extended	MF(ACI)

					dominated	
ACI (ACI)	[redacted]	18.0121	[redacted]	0.1011	[redacted]	MF(ACI)

Note that in this and subsequent analysis of price changes, the QALY gain does not change in the determistic arms, as expected. However when the model is run probabilistically all the input variables change due to the different distributions hence both the costs and QALYs will change.

Figure 17 Cost-effectiveness acceptability curve (PAS)

3.2.2 Lower price

Data used for ACI failure rates: Nawaz[23] (whole cohort)

Data used for MF failure rates: Pooled data (Layton[20], Knutsen[19], Saris[46])

Cost of harvesting: £870

Cost of implantation: £2,396

Cost of cells: £6,000

Table 9 Deterministic and probabilistic cost-effectiveness results (£6,000 price)

Procedure	Total mean costs £	Total mean QALYs	Incremental costs £	Incremental QALYs	ICER versus MF(ACI)	Comparator
Deterministic - undiscounted						
MF (ACI)	6,771	34.2885	-	-	-	-
ACI (MF)	12,661	35.5596	5,890	1.2711	Extended dominated	MF(ACI)
ACI (ACI)	13,244	35.6999	583	0.1403	4,586	MF(ACI)

Deterministic – discounted						
MF (ACI)	5,441	17.1350	-	-	-	-
ACI (MF)	11,400	17.9304	5,959	0.7954	Extended dominated	MF(ACI)
ACI (ACI)	11,820	17.9953	420	0.0650	7,414	MF(ACI)
Probabilistic – discounted						
MF (ACI)	5,452	17.1340	-	-	-	-
ACI (MF)	11,486	17.9110	6,034	0.7770	7,766	MF(ACI)
ACI (ACI)	11,909	17.9474	423	0.0364	11,622	ACI(MF)

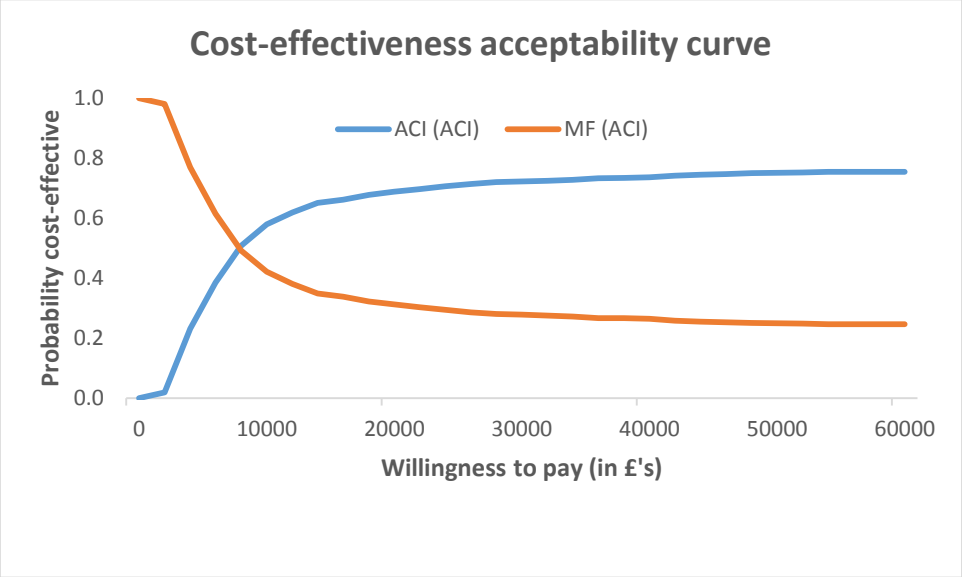


Figure 18 Cost-effectiveness acceptability curve (£6,000)

3.3 Sensitivity analyses (Post-repair utility)

In our first assessment report, we assumed that patients who decided not to have a further repair, had had some benefit, and had improved from a utility of 0.654 before the repair to 0.691 afterwards. NICE asked us to assess the effect of several assumptions for utilities in those in whom repair in unsuccessful but who choose not to have another operation.

3.3.1 Utility for choose no second repair set to same as failure

Data used for ACI failure rates: Nawaz[23](whole cohort)

Data used for MF failure rates: Pooled data (Layton[20], Knutsen[19], Saris[46])

Cost of harvesting: £870

Cost of implantation: £2,396

Cost of cells: £16,000

Utility for those who choose no second repair: 0.654

Table 10 Deterministic and probabilistic cost-effectiveness results (Utility = 0.654)

Procedure	Total mean costs £	Total mean QALYs	Incremental costs £	Incremental QALYs	ICER versus MF(ACI)	Comparator
Deterministic - undiscounted						
MF (ACI)	7,736	32.8665	-	-	-	-
ACI (MF)	22,661	34.4351	14,926	1.5686	Extended dominated	MF(ACI)
ACI (ACI)	24,134	34.6021	1,473	0.1670	9,449	MF(ACI)
Deterministic – discounted						
MF (ACI)	6,248	16.5058	-	-	-	-
ACI (MF)	21,400	17.4667	15,152	0.9609	Extended dominated	MF(ACI)
ACI (ACI)	22,461	17.5428	1,062	0.0762	15,634	MF(ACI)
Probabilistic – discounted						
MF (ACI)	6,253	16.4140	-	-	-	-
ACI (MF)	21,321	17.4607	15,068	1.0467	Extended dominated	MF(ACI)
ACI (ACI)	22,388	17.5612	1,066	0.1005	14,064	MF(ACI)

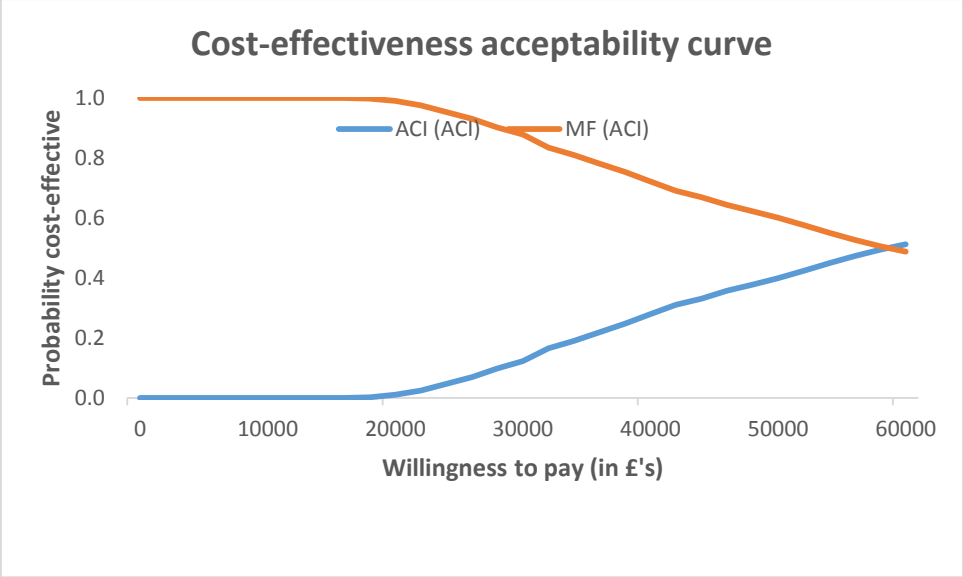


Figure 19 Cost-effectiveness acceptability curve (util = 0.654)

3.3.2 Utility for choose no second repair set to same as success

Data used for ACI failure rates: Nawaz[23] (whole cohort)

Data used for MF failure rates: Pooled data (Layton[20], Knutsen[19], Saris[46])

Cost of harvesting: £870

Cost of implantation: £2,396

Cost of cells: £16,000

Utility for those who choose no second repair: 0.817. Note that this assumption greatly increases utility gain amongst those who do not get good results after MF, and reduces the marginal QALY gains from ACI.

Table 11 Deterministic and probabilistic cost-effectiveness results (Utility = 0.817**)**

Procedure	Total mean costs £	Total mean QALYs	Incremental costs £	Incremental QALYs	ICER versus MF(ACI)	Comparator
Deterministic - undiscounted						
MF (ACI)	7,736	39.1309	-	-	-	-
ACI (MF)	22,661	39.3889	14,926	0.2580	Extended dominated	MF(ACI)
ACI (ACI)	24,134	39.4383	1,473	0.0494	53,352	MF(ACI)
Deterministic – discounted						
MF (ACI)	6,248	19.2776	-	-	-	-
ACI (MF)	21,400	19.5096	15,152	0.2320	Extended dominated	MF(ACI)
ACI (ACI)	22,461	19.5363	1,062	0.0267	62,658	MF(ACI)
Probabilistic – discounted						
MF (ACI)	6,246	19.2749	-	-	-	-
ACI (MF)	21,416	19.5039	15,171	0.2290	Extended dominated	MF(ACI)
ACI (ACI)	22,484	19.5423	1,068	0.0384	60,716	MF(ACI)

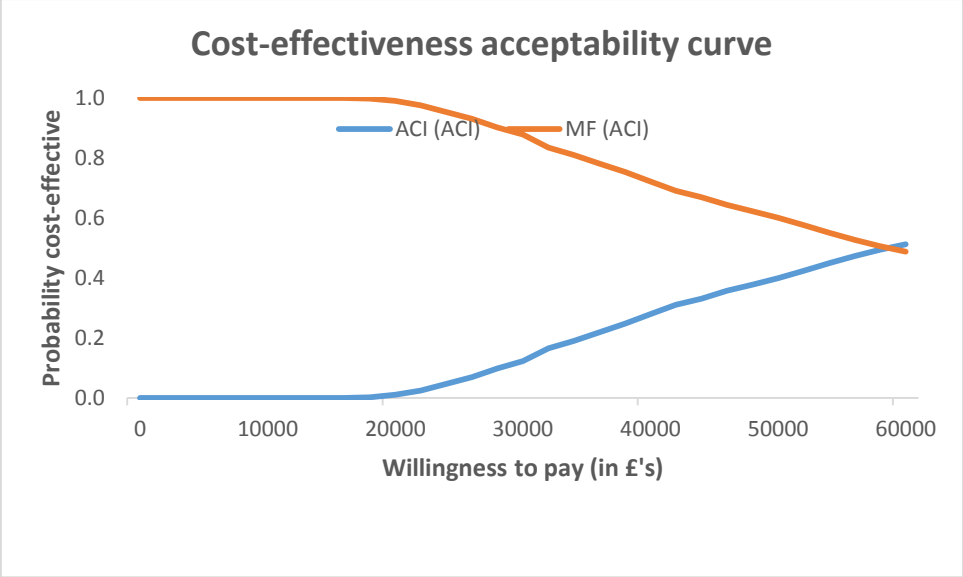


Figure 20 Cost-effectiveness acceptability curve (util = 0.817)

3.3.3 Utility for choose no second repair set to mid-point of success and failure

Data used for ACI failure rates: Nawaz [23](whole cohort)

Data used for MF failure rates: Pooled data (Layton[20], Knutsen[19], Saris[46])

Cost of harvesting: £870

Cost of implantation: £2,396

Cost of cells: £16,000

Utility for those who choose no second repair: 0.746. This also reduces the marginal QALY gains from ACI as first procedure, because the larger proportion which does not do well after MF, have their utility increased.

Table 12 Deterministic and probabilistic cost-effectiveness results (Utility = 0.746)

Procedure	Total mean costs £	Total mean QALYs	Incremental costs £	Incremental QALYs	ICER versus MF(ACI)	Comparator
Deterministic - undiscounted						
MF (ACI)	7,736	36.4022	-	-	-	-
ACI (MF)	22,661	37.2311	14,926	0.8289	Extended dominated	MF(ACI)
ACI (ACI)	24,134	37.3317	1,473	0.1006	17,643	MF(ACI)
Deterministic – discounted						
MF (ACI)	6,248	18.0702	-	-	-	-
ACI (MF)	21,400	18.6197	15,152	0.5495	Extended dominated	MF(ACI)
ACI (ACI)	22,461	18.6680	1,062	0.0483	27,123	MF(ACI)
Probabilistic – discounted						
MF (ACI)	6,248	18.0400	-	-	-	-
ACI (MF)	21,419	18.6257	15,171	0.5857	Extended dominated	MF(ACI)
ACI (ACI)	22,496	18.6684	1,077	0.0427	25,857	MF(ACI)

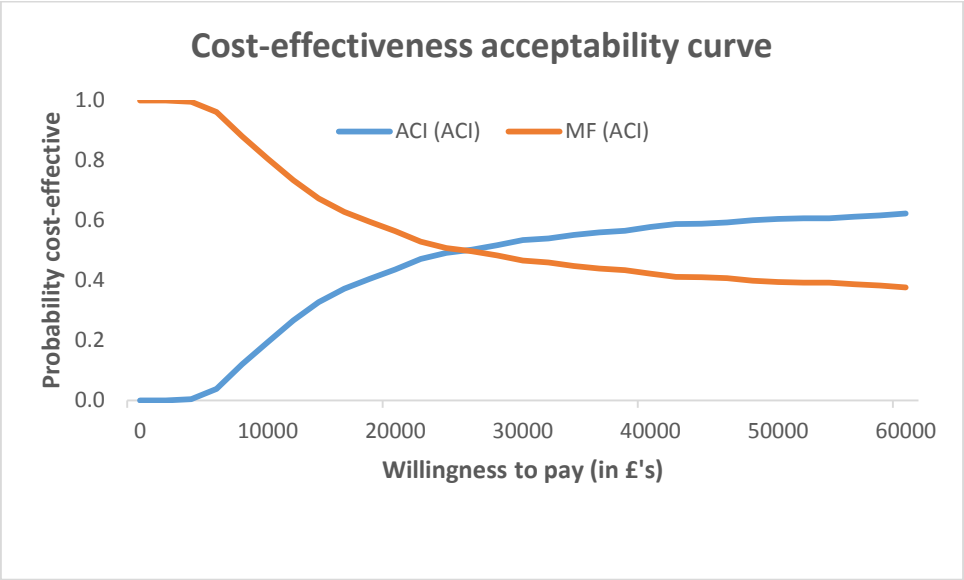


Figure 21 Cost-effectiveness acceptability curve (util = 0.746)

3.4 Subgroup analyses

3.4.1 Individuals with prior repair attempts

Data used for ACI failure rates: Nawaz[23] (previous intervention)

Data used for MF failure rates: Pooled data (Layton[20], Knutsen[19], Saris[46])

Cost of harvesting: £870

Cost of implantation: £2,396

Cost of cells: £16,000

Table 13 Deterministic and probabilistic cost-effectiveness results (previous intervention)

Procedure	Total mean costs £	Total mean QALYs	Incremental costs £	Incremental QALYs	ICER versus MF(ACI)	Comparator
Deterministic - undiscounted						
MF (ACI)	7,736	34.2885	-	-	-	-
ACI (MF)	22,718	34.7835	14,983	0.4950	Extended dominated	MF(ACI)
ACI (ACI)	24,314	34.9315	1,595	0.1480	25,780	MF(ACI)
Deterministic – discounted						
MF (ACI)	6,248	17.1350	-	-	-	-
ACI (MF)	21,462	17.4918	15,214	0.3569	Extended dominated	MF(ACI)
ACI (ACI)	22,746	17.5661	1,284	0.0743	38,262	MF(ACI)
Probabilistic – discounted						
MF (ACI)	6,236	17.1315	-	-	-	-
ACI (MF)	21,503	17.4889	15,267	0.3575	Extended dominated	MF(ACI)
ACI (ACI)	22,798	17.5522	1,295	0.0632	39,370	MF(ACI)

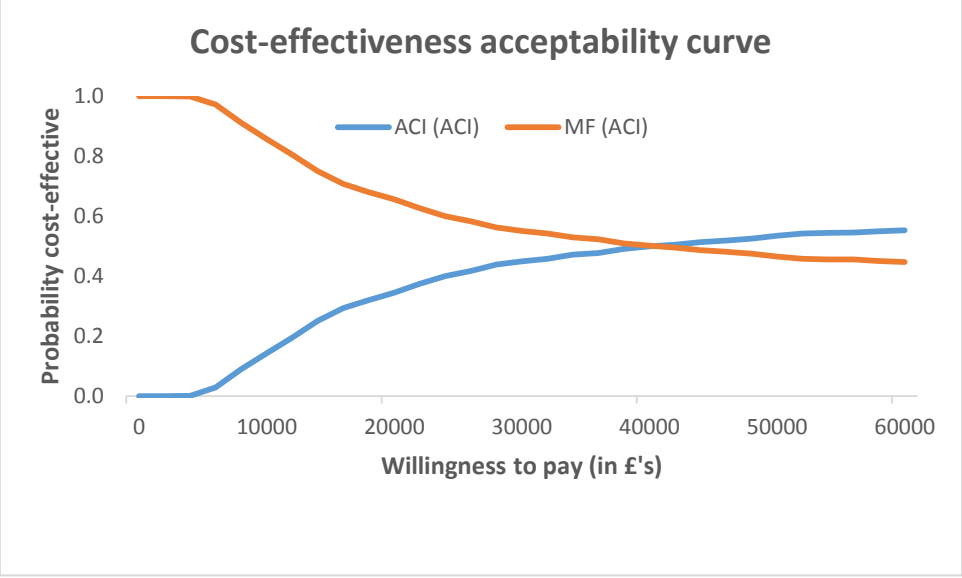


Figure 22 Cost-effectiveness acceptability curve (previous interventions)

Individuals without prior repair attempts
Data used for ACI failure rates: Nawaz [23](no previous intervention)

Data used for MF failure rates: Pooled data (Layton[20], Knutsen[19], Saris[46])

Cost of harvesting: £870

Cost of implantation: £2,396

Cost of cells: £16,000

Table 14 Deterministic and probabilistic cost-effectiveness results (no previous intervention)

Procedure	Total mean costs £	Total mean QALYs	Incremental costs £	Incremental QALYs	ICER versus MF(ACI)	Comparator
Deterministic - undiscounted						
MF (ACI)	7,736	34.2885	-	-	-	-
ACI (MF)	21,956	37.4216	14,220	3.1332	4,539	MF(ACI)
ACI (ACI)	22,826	37.5038	870	0.0822	10,586	ACI(MF)
Deterministic – discounted						
MF (ACI)	6,248	17.1350	-	-	-	-
ACI (MF)	21,101	18.7446	14,853	1.6097	9,227	MF(ACI)
ACI (ACI)	21,644	18.7793	543	0.0347	15,659	ACI(MF)
Probabilistic – discounted						
MF (ACI)	6,268	17.1506	-	-	-	-
ACI (MF)	21,114	18.6100	14,846	1.4594	10,172	MF(ACI)
ACI (ACI)	21,930	18.6411	816	0.0310	26,324	ACI(MF)

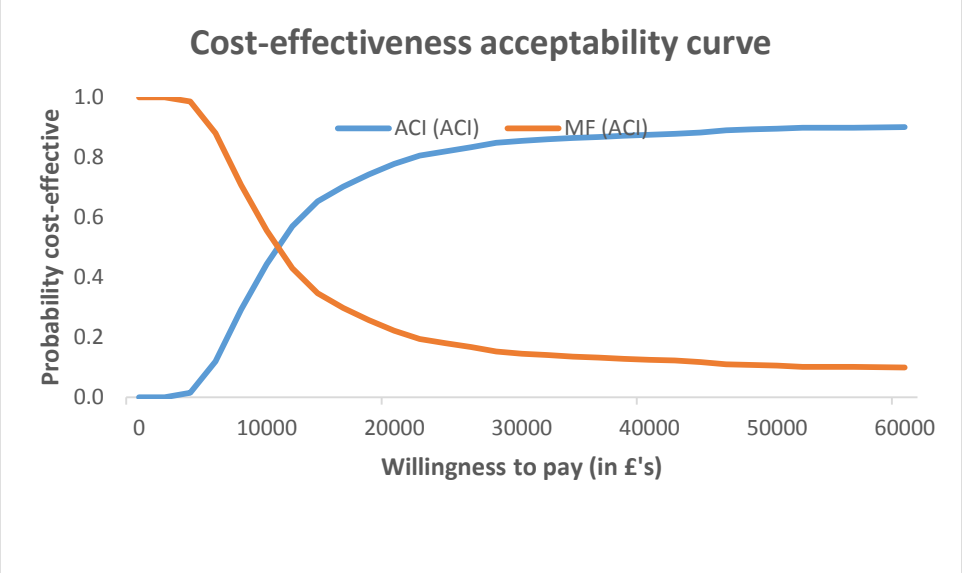


Figure 23 Cost-effectiveness acceptability curve (no previous interventions)

3.4.2 Individuals with Kellgren grade 0

Data used for ACI failure rates: Nawaz[23] (Kellgren grade 0)

Data used for MF failure rates: Pooled data (Layton[20], Knutsen[19], Saris[46])

Cost of harvesting: £870

Cost of implantation: £2,396

Cost of cells: £16,000

Table 15 Deterministic and probabilistic cost-effectiveness results (Kellgren grade 0)

Procedure	Total mean costs £	Total mean QALYs	Incremental costs £	Incremental QALYs	ICER versus MF(ACI)	Comparator
Deterministic - undiscounted						
MF (ACI)	7,736	34.2885	-	-	-	-
ACI (MF)	22,489	36.4611	14,753	2.1726	6,791	MF(ACI)
ACI (ACI)	23,727	36.5794	1,238	0.1183	10,470	ACI(MF)
Deterministic – discounted						
MF (ACI)	6,248	17.1350	-	-	-	-
ACI (MF)	21,294	18.3745	15,046	1.2395	12,138	MF(ACI)
ACI (ACI)	22,079	18.4247	785	0.0503	15,618	ACI(MF)

3.4.3 Individuals with Kellgren grade 1

Data used for ACI failure rates: Nawaz [23](Kellgren grade 1)

Data used for MF failure rates: Pooled data (Layton[20], Knutsen[19], Saris[46])Cost of harvesting: £870

Cost of implantation: £2,396

Cost of cells: £16,000

Table 16 Deterministic and probabilistic cost-effectiveness results (Kellgren grade 1)

Procedure	Total mean costs £	Total mean QALYs	Incremental costs £	Incremental QALYs	ICER versus MF(ACI)	Comparator
Deterministic - undiscounted						
MF (ACI)	7,736	34.2885	-	-	-	-
ACI (MF)	22,679	35.7135	14,943	1.4250	10,486	MF(ACI)
ACI (ACI)	24,129	35.8516	1,450	0.1381	10,499	ACI(MF)
Deterministic – discounted						
MF (ACI)	6,248	17.1350	-	-	-	-
ACI (MF)	21,395	18.0173	15,147	0.8824	Extended dominated	MF(ACI)
ACI (ACI)	22,408	18.0798	1,013	0.0624	17,104	MF(ACI)

3.4.4 Individuals with Kellgren grade 2

Data used for ACI failure rates: Nawaz[23] (Kellgren grade 2)

Data used for MF failure rates: Pooled data (Layton[20], Knutsen[19], Saris[46])

Cost of harvesting: £870

Cost of implantation: £2,396

Cost of cells: £16,000

Table 17 Deterministic and probabilistic cost-effectiveness results (Kellgren grade 2)

Procedure	Total mean costs £	Total mean QALYs	Incremental costs £	Incremental QALYs	ICER versus MF(ACI)	Comparator
Deterministic - undiscounted						
MF (ACI)	7,736	34.2885	-	-	-	-
ACI (MF)	22,718	35.4402	14,983	1.1517	Extended dominated	MF(ACI)
ACI (ACI)	24,233	35.5842	1,514	0.1440	12,732	MF(ACI)
Deterministic – discounted						
MF (ACI)	6,248	17.1350	-	-	-	-
ACI (MF)	21,423	17.8779	15,175	0.7430	Extended dominated	MF(ACI)
ACI (ACI)	22,520	17.9447	1,097	0.0667	20,096	MF(ACI)

3.4.5 Individuals with Kellgren grade 3

Data used for ACI failure rates: Nawaz[23] (Kellgren grade 3)

Data used for MF failure rates: Pooled data (Layton[20], Knutsen[19], Saris[46])

Cost of harvesting: £870

Cost of implantation: £2,396

Cost of cells: £16,000

Table 18 Deterministic and probabilistic cost-effectiveness results (Kellgren grade 3)

Procedure	Total mean costs £	Total mean QALYs	Incremental costs £	Incremental QALYs	ICER versus MF(ACI)	Comparator
Deterministic - undiscounted						
MF (ACI)	7,736	34.2885	-	-	-	-
ACI (MF)	22,726	35.3609	14,990	1.0724	Extended dominated	MF(ACI)
ACI (ACI)	24,258	35.5063	1,532	0.1455	13,566	MF(ACI)
Deterministic – discounted						
MF (ACI)	6,248	17.1350	-	-	-	-
ACI (MF)	21,430	17.8358	15,183	0.7008	Extended dominated	MF(ACI)
ACI (ACI)	22,552	17.9038	1,122	0.0680	21,207	MF(ACI)

3.5 Sensitivity analyses

3.5.1 Pooled ACI curve (6 studies)

Data used for ACI failure rates: Pooled data (Knutsen[19], Minas [44], Mosely[22], Nawaz,[23] Niemeyer[25], Vanlauwe[1])

Data used for MF failure rates: Pooled data (Layton[20], Knutsen[19], Saris[46])

Cost of harvesting: £870

Cost of implantation: £2,396

Cost of cells: £16,000

Table 19 Deterministic and probabilistic cost-effectiveness results (6 ACI datasets)

Procedure	Total mean costs £	Total mean QALYs	Incremental costs £	Incremental QALYs	ICER versus MF(ACI)	Comparator
Deterministic - undiscounted						
MF (ACI)	7,736	34.2885	-	-	-	-
ACI (MF)	22,140	36.7771	14,405	2.4886	5,788	MF(ACI)
ACI (ACI)	23,195	37.8748	1,055	0.0978	10,794	ACI(MF)
Deterministic – discounted						
MF (ACI)	6,248	17.1350	-	-	-	-
ACI (MF)	21,192	18.4290	14,944	1.2940	11,549	MF(ACI)
ACI (ACI)	21,933	18.4734	741	0.0444	16,708	ACI(MF)
Probabilistic – discounted						
MF (ACI)	6,271	17.1731	-	-	-	-
ACI (MF)	21,235	18.4253	14,964	1.2522	11,950	MF(ACI)
ACI (ACI)	21,991	18.4948	757	0.0695	10,882	ACI(MF)

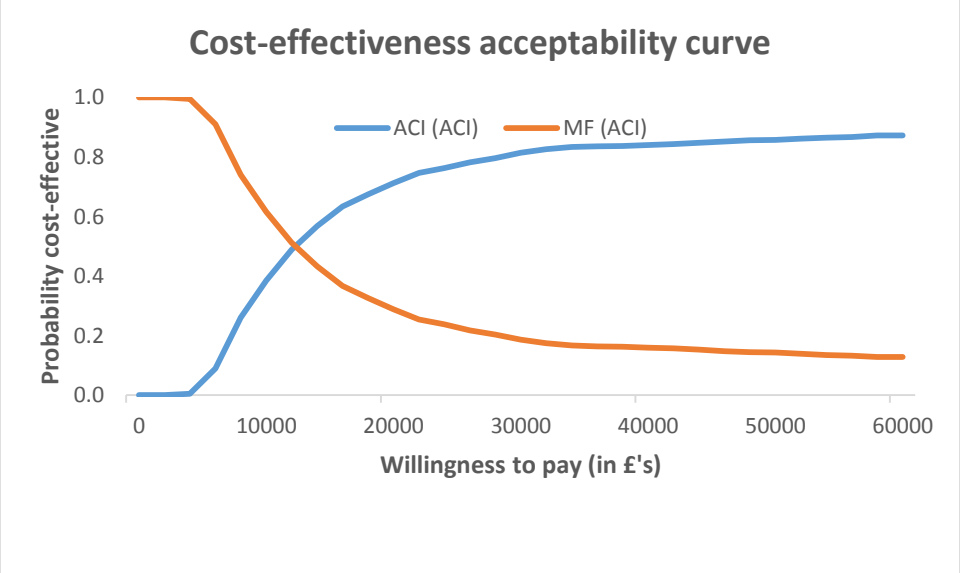


Figure 24 Cost-effectiveness acceptability curve (6 ACI datasets)

3.5.2 Pooled ACI curve (7 studies)

Data used for ACI failure rates: Pooled data (ACTIVE, Knutsen[47], Minas[44], Mosely[22], Nawaz[23], Niemeyer[25], Vanlauwe[1])

Data used for MF failure rates: Pooled data (Layton[20], Knutsen[47], Saris[46])

Cost of harvesting: £870

Cost of implantation: £2,396

Cost of cells: £16,000

Table 20 Deterministic and probabilistic cost-effectiveness results (7 ACI datasets)

Procedure	Total mean costs £	Total mean QALYs	Incremental costs £	Incremental QALYs	ICER versus MF(ACI)	Comparator
Deterministic - undiscounted						
MF (ACI)	7,736	34.2885	-	-	-	-
ACI (MF)	22,361	36.4134	14,625	2.1249	6,883	MF(ACI)
ACI (ACI)	23,635	36.5298	1,275	0.1164	10,951	ACI(MF)
Deterministic – discounted						
MF (ACI)	6,248	17.1350	-	-	-	-
ACI (MF)	21,288	18.2802	15,040	1.1452	13,133	MF(ACI)
ACI (ACI)	22,211	18.3335	923	0.0533	17,325	ACI(MF)

3.5.3 Cells at cost £8,000

Data used for ACI failure rates: Nawaz (whole cohort)

Data used for MF failure rates: Pooled data (Layton[20], Knutsen [47], Saris[46])

Cost of harvesting: £870

Cost of implantation: £2,396

Cost of cells: £8,000

Table 21 Deterministic and probabilistic cost-effectiveness results (£8,000 price)

Procedure	Total mean costs £	Total mean QALYs	Incremental costs £	Incremental QALYs	ICER versus MF(ACI)	Comparator
Deterministic – undiscounted						
MF (ACI)	6,964	34.2885	-	-	-	-
ACI (MF)	14,661	35.5596	7,697	1.2711	Extended dominated	MF(ACI)
ACI (ACI)	15,422	35.6999	761	0.1403	5,993	MF(ACI)
Deterministic – discounted						
MF (ACI)	5,602	17.1350	-	-	-	-
ACI (MF)	13,400	17.9304	7,797	0.7954	Extended dominated	MF(ACI)
ACI (ACI)	13,948	17.9953	549	0.0650	9,700	MF(ACI)
Probabilistic – discounted						
MF (ACI)	5,608	17.1630	-	-	-	-
ACI (MF)	13,430	17.9500	7,822	0.7871	9,938	MF(ACI)
ACI (ACI)	13,983	18.0242	553	0.0742	7,454	ACI(MF)

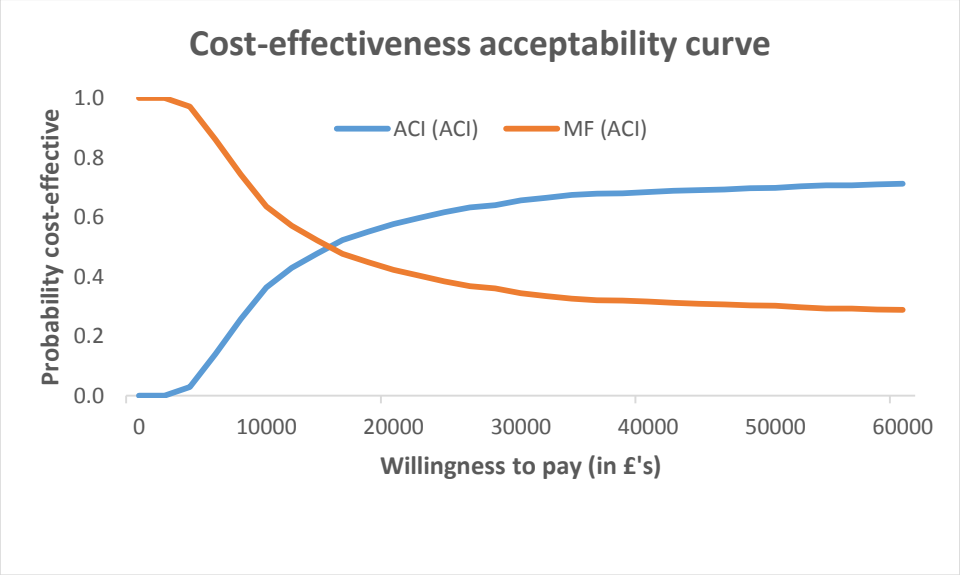


Figure 25 Cost-effectiveness acceptability curve (£8,000)

3.5.4 Cells at cost of £12,000

Data used for ACI failure rates: Nawaz (whole cohort)

Data used for MF failure rates: Pooled data (Layton[20], Knutsen [47], Saris[46])

Cost of harvesting: £870

Cost of implantation: £2,396

Cost of cells: £12,000

Table 22 Deterministic and probabilistic cost-effectiveness results (£12,000 price)

Procedure	Total mean costs £	Total mean QALYs	Incremental costs £	Incremental QALYs	ICER versus MF(ACI)	Comparator
Deterministic – undiscounted						
MF (ACI)	7,350	34.2885	-	-	-	-
ACI (MF)	18,661	35.5596	11,312	1.2711	Extended dominated	MF(ACI)
ACI (ACI)	19,778	35.6999	1,117	0.1403	8,806	MF(ACI)
Deterministic – discounted						
MF (ACI)	5,925	17.1350	-	-	-	-
ACI (MF)	17,400	17.9304	11,475	0.7954	Extended dominated	MF(ACI)
ACI (ACI)	18,205	17.9953	805	0.0650	14,272	MF(ACI)
Probabilistic – discounted						
MF (ACI)	5,918	17.1425	-	-	-	-
ACI (MF)	17,320	17.9539	11,402	0.8114	Extended Dominated	MF(ACI)
ACI (ACI)	18,131	17.9899	811	0.0360	14,412	MF(ACI)

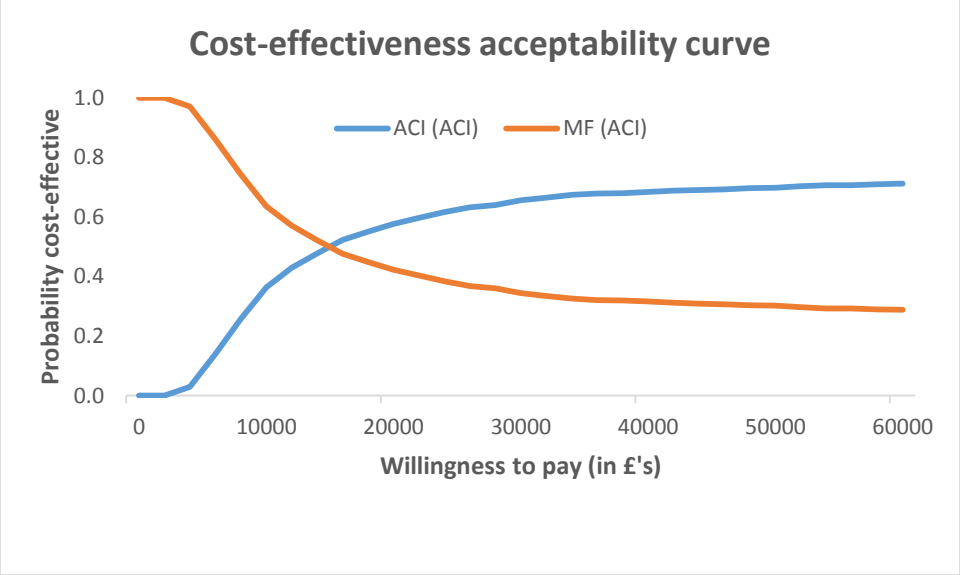


Figure 26 Cost-effectiveness acceptability curve (£12,000)

3.6 Using utility data from Vericel

Data used for ACI failure rates: Nawaz (whole cohort)

Data used for MF failure rates: Pooled data (Layton[20], Knutsen [47], Saris[46])

Table 23 Utility data from Vericel

	MACI	**MF**
Baseline N Mean utility value (SD)	141 0.484 (0.296)	
Response at week 52 N Mean utility value (SD)	71 0.7848 (0.2113)	68 0.7472 (0.2270)
Response at week 104 N Mean utility value (SD)	70 0.8051 (0.1899)	70 0.7188 (0.2969)
Response at week 156 N Mean utility value (SD)	65 0.8131 (0.2105)	59 0.7769 (0.2553)

Table 24 Deterministic and probabilistic cost-effectiveness results

Procedure	**Total mean costs £**	**Total mean QALYs**	**Incremental costs £**	**Incremental QALYs**	**ICER versus MF(ACI)**	**Comparator**
Deterministic - undiscounted						
MF (ACI)	7,736	33.8297	-	-	-	-
ACI (MF)	22,661	35.2364	14,926	1.4067	Extended dominated	MF(ACI)
ACI (ACI)	24,134	35.3784	1,473	0.1420	10,588	MF(ACI)
Deterministic – discounted						
MF (ACI)	6,248	16.6956	-	-	-	-
ACI (MF)	21,400	17.6627	15,152	0.9671	Extended dominated	MF(ACI)
ACI (ACI)	22,461	17.7317	1,061	0.0690	15,648	MF(ACI)
Probabilistic – discounted						
MF (ACI)	6,283	16.7221	-	-	-	-
ACI (MF)	21,381	17.6499	15,098	0.9277	Extended dominated	MF(ACI)
ACI (ACI)	22,456	17.7528	1,075	0.1029	15,692	MF(ACI)

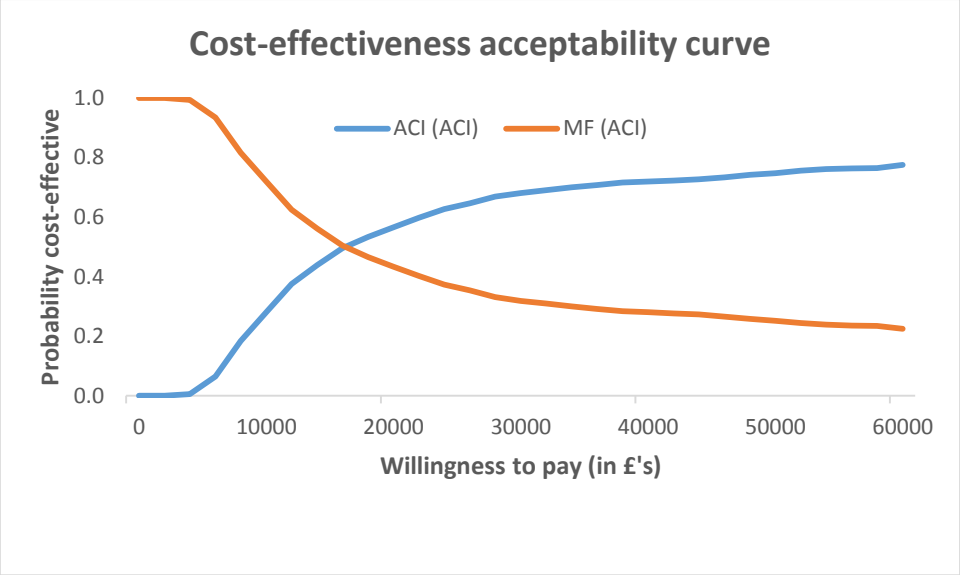


Figure 27 Cost-effectiveness acceptability curve

3.7 Summary comments

- In many scenarios, ACI (MF) is extended dominated, meaning that the relevant choice is between ACI (ACI) and MF (ACI), and the use of microfracture as a post-ACI treatment is not a relevant alternative.
- The exceptions to this tend to be in scenarios where ACI is particularly effective (e.g. no previous repair, Kellgren grade of 0) where there is less additional benefit to be gained from a more effective second procedure.
- Decreases in ACI treatment costs, unsurprisingly, lead to reductions in the ICERs for ACI.
- Higher utilities in the "no further treatment" state make ACI less cost-effective, as there is less benefit gained from successful procedures, and likewise lower utilities in the "no further treatment" state make ACI more cost-effective.
- Including evidence from a wider range of studies make ACI appear more cost-effective than using data from Nawaz alone.
- The exception to this is the inclusion of data from the ACTIVE study, which makes ACI appear less cost-effective.

4 SOBI submission

4.1 Commentary on Sobi submission Oct 2015: Survival analysis.

Sobi pooled reconstructed IPD for 5 ACI studies which provided data beyond five years. The studies varied in failure definition and proportion of patients previously treated. Parametric models were fitted and according to information criteria, the best fit was from a Gompertz model followed by Gamma model. These studies encompassed 507 patients, and included one study with 62 participants not included by the Assessment Group. This study was by Filardo and colleagues [48] who were using the Hyalograft scaffold, which is a bio-engineered non-collagen product, which was excluded by the AG. Hyalograft was withdrawn from the market in January 2013. Sobi excluded the largest relevant study (Nawaz 2014 [23]) with 827 patients, which the AG think is the most relevant study because it was undertaken with UK patients, had a mix of ACI-generations and patients, and provided subgroup analyses. Also excluded were arms of studies with data to five years. When the six ACI studies with 5 years or more follow up that were identified by the AG are pooled the best fits is provided by a gamma model.

Table 25 Information criteria for 6 studies with ACI arms examined in the Assessment group report

Model	Obs	ll(model)	df	AIC	BIC
gamma	1270	-975.825	3	1957.649	1973.09
exponential	1270	-1013.96	1	2029.922	2035.069
weibull	1270	-1006.09	2	2016.178	2026.472
gompertz	1270	-1013.86	2	2031.712	2042.005
lognormal	1270	-982.15	2	1968.301	1978.594
loglogistic	1270	-993.514	2	1991.028	2001.321

Figure 28 shows the Kaplan Meier plot and best fit gamma model (95% CI) to 70 years post intervention for the pooled 6 ACI studies (Knutsen[19], Vanlauwe[1], Nawaz[23], Niemeyer[25], Minas[44], Moseley[22]), together with the Sobi best and worst scenario models based on 5 ACI studies.

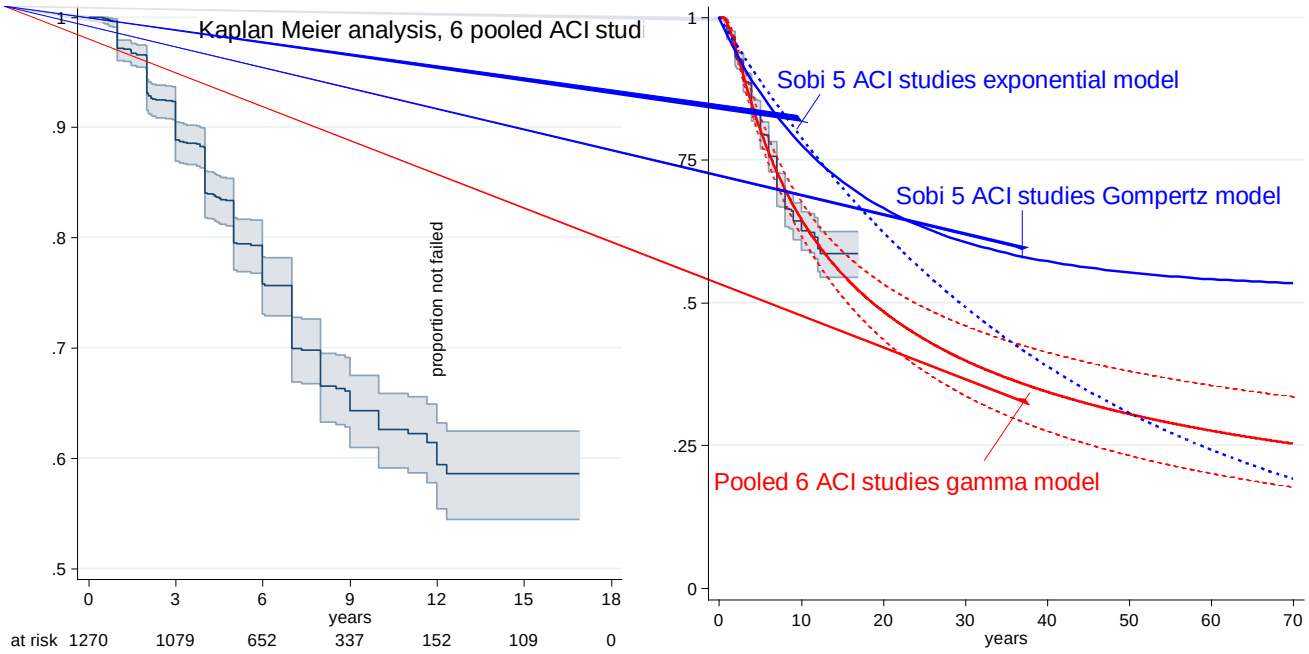


Figure 28 Pooled ACI studies compared to SoBi curves

The gamma model for six studies generates poorer survival than the Gompertz model generated by Sobi for five pooled studies.

Alternative models for the 6 pooled studies are shown in Figure 29. It is moot question whether pooling the five ACI studies of Sobi or all eight AG-identified studies is justified.

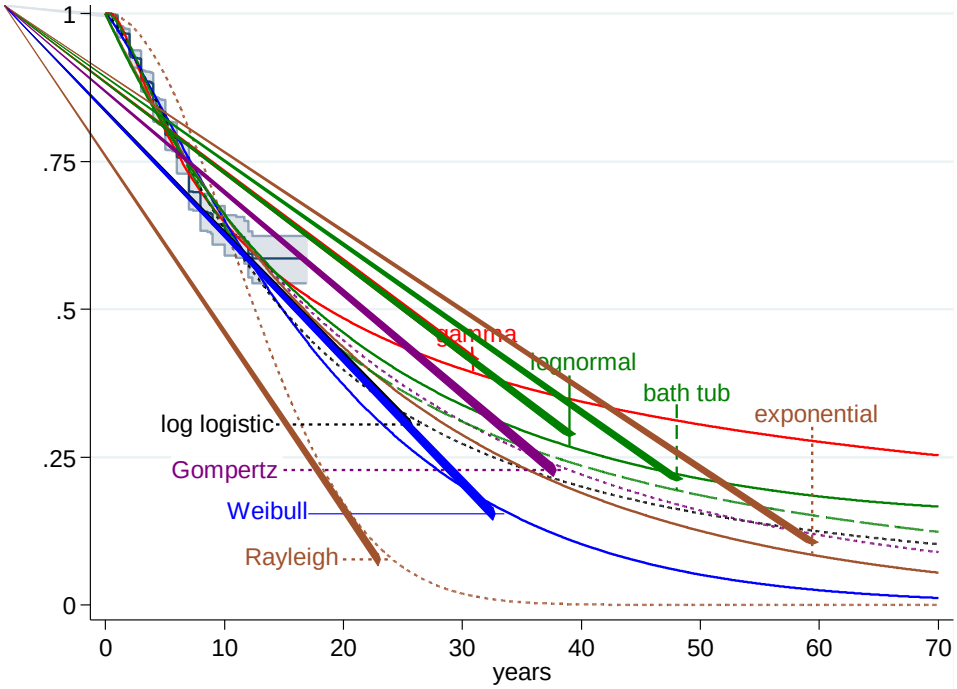


Figure 29 Alternative models for pooled studies.

For the purposes of base case economic modelling Sobi used the Gompertz fits to 5 pooled studies to develop a model of failure of ACI for times beyond the 71 months of observed data (Kaplan Meier) from the Vanlauwe TIG/ACI/01 study (Figure 30). The TIG/ACI/01 study included only 51 patients in ACI arm and it might be suggested that using the pooled data for all the ACI arms would be more appropriate. The resulting hybrid curve generated by Sobi incorporates data for 51 patients to 71 months and an extrapolation based on a Gompertz curve that excluded these 51 patients. The resulting hybrid may be considered to probably flatter ACI in that the major Nawaz study[23] has been excluded.

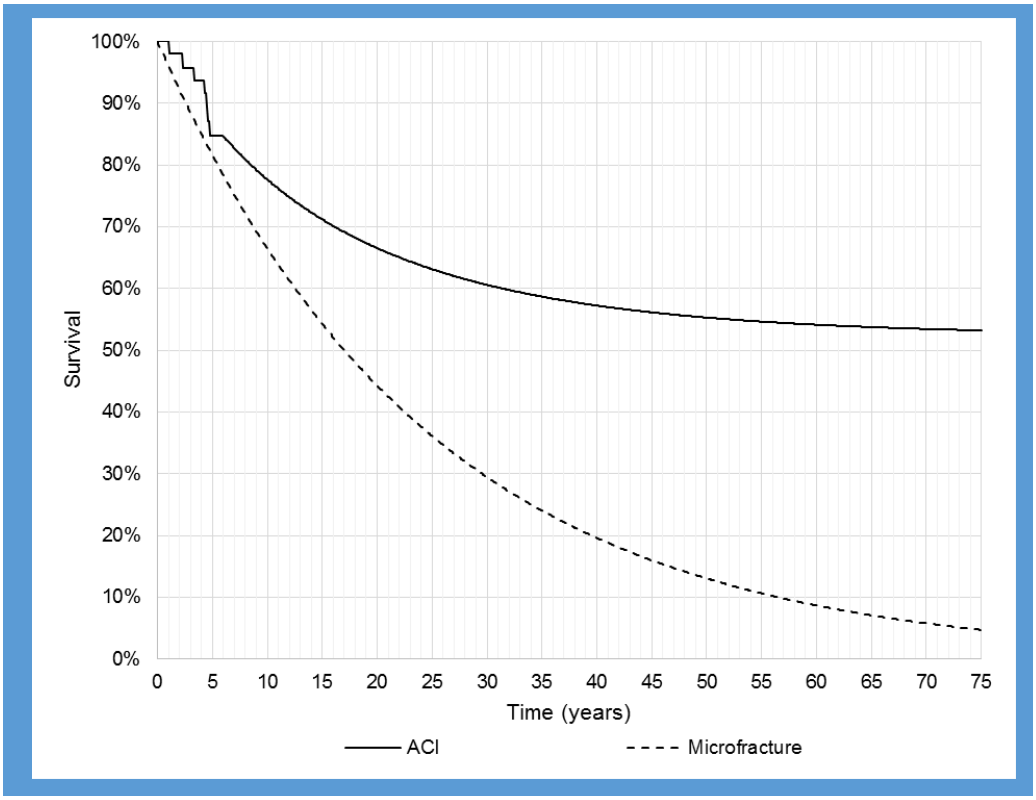


Figure 30 SoBi hybrid curve for ACI failure (TIG/ACI/01 KM to 70 months, then a Gompertz model for 5 pooled ACI studies). Also shown is the SoBi MF failure model based on an expontntial fit to the MF arm of the TIG/ACI/01 study.

Sobi have not pooled microfracture studies. For the comparator microfracture arm the new submission appears to have used an exponential survival curve based on the MF arm of the TIG/ACI/01 study as in a previous submission, however this is unclear.

The Assessment group found an anomaly in the published risk table for the microfracture arm of the TIG/ACI/01 study. A speculative correction to the risk table (see Appendix 7) allowed reconstruction of IPD which yielded the exponential model shown in Figure 31 left. This plot is closely similar to that proposed by SoBi. Alternative candidate models (Figure 31 right) produce variously different

models of failure. The small number of patients and apparent anomaly in published data render these curves problematical.

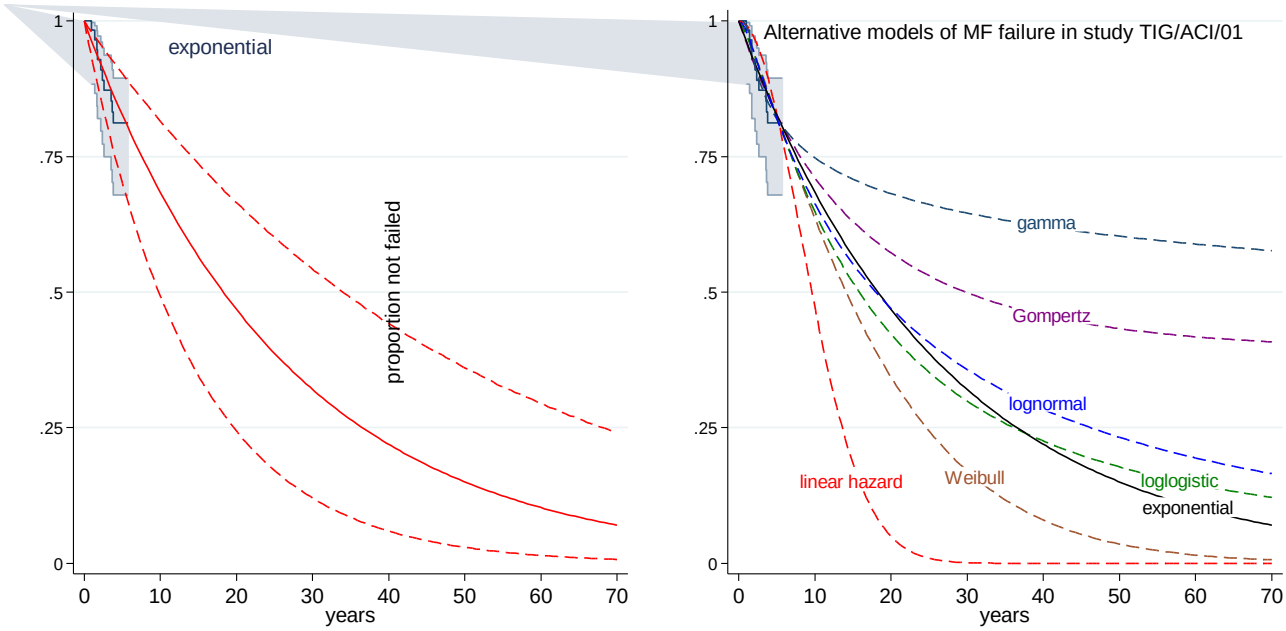


Figure 31 Exponential and other parametric models of MF failure based on the MF arm of study TIG/ACI/01

Based on their pooled studies, the SOBI analysis concludes that survival of ACI was 70% after 15 years. Applying their long-term survival data in the modelling reduces the ICER from about £26,000 to £21,000, and adding the PAS reduces this to about [redacted]

The weakness in the SoBi analysis is the lack of similar survival analysis for microfracture, but that is partly because there are fewer long-term studies of microfracture than of ACI.

5 Discussion

5.1 Main findings

There is a shortage of long-term studies, particularly of microfracture. As requested by NICE, we carried out survival analysis making the best of what data there were. Caveats follow.

We included six studies of long-term results of ACI, the best of which was by Nawaz and colleagues[23], from Stanmore. It was best because of size (827 – all the other studies put together provided 371), because it reflected UK practice (albeit from a centre of excellence), because it provided data from the period 1998 to 2008, on different generations of ASCI, and because it provided very useful subgroup data.

Using the older data, microfracture comes out less well, with progressive failure over time.
As noted in the previous report, ACI is less successful in people who had had prior repair attempts such as microfracture.

5.2 Limitations

When considering survival curves extrapolated beyond the observed data, it should be borne in mind that the extrapolation assumes that the curve based on the observed data will continue. However this may not always be the case. For example, if ACI failures occurred mainly in the early observed years, longer term observations would show a levelling off. However this may only apply after successful ACI. Bhosale and colleagues from Oswestry[13] in a series of 80 patients reported that success at 15 months was sustained, but average follow-up was only for 5 years. The Nawaz study[23] suggests that when ACI is most successful, the survival curve shows some leveling off by about 7 years, whereas in those in whom it fails, the curve shows a linear decline.

The lack of data on the benefits of microfracture compared to debridement alone is a problem. (And it is worth remembering that in a previous assessment report, we noted a lack of evidence for debridement and lavage over non-operative approaches.[49])

We relied heavily on the Nawaz study [23]. We confirmed with the lead author that the patients in the ACI arm of the Bentley trial [11], and the cohort in the long-term outcome study by Biant and colleagues [14], were included. Before obtaining that information, we had included the Bentley and Biant studies on pooled survival analysis. Curiously, removing them worsened the ACI results,

despite them having in some ways, patients with poorer prognostic factors. For example, the proportions having previous repair attempts were 34% in Nawaz, 94% in Bentley and 73% in Biant. The patients in the Bentley and Biant studies were from the earliest days (1998-2001), and were "salvage" cases after means of 1.7 and 1.3 previous procedures.

The reason for the better results in the Minas series [44] than in the Nawaz study is not clear. The Minas patients all had MACI. The defintions of failure may explain some of the difference, with failure in Minas very surgically defined, such that some failures in the Nawaz study might not have been classed as failure by Minas et al.

Another variable that may cause differences in outcomes could be differences in comparator treatments such as drilling and microfracture. After MF, microscopic cracks form around the holes. These do not occur when bone is drilled. So MF may do more damage to the subchondral bone.

As noted, there are rather more long-term studies of ACI than of MF. Why are there so few of MF? Could it be that long-term results are poor and that people with data do not publish it? Should the questions in this appraisal have included: Should microfracture be done at all, irrespective of whether ACI is available?

5.3 ACI and osteoarthritis

As noted earlier, results of ACI are poorer in people with osteoarthritis, especially more advanced grades, using the Kellgren-Lawrence grading system. However, if ACI were to be restricted based on radiological signs of OA, there are some problems to be considered.

One of the difficulties in comparing the results of studies involving patients with osteoarthritis is the definition of the disease and the assessment of its severity. The EULAR definition of osteoarthritis emphasises the importance of pain and functional loss alongside physical changes in the joint, but this definition is hard to objectively apply in research terms and symptoms are significantly influenced by environmental and psychosocial factors.[50-53]

There is a variable relationship between symptoms and structural changes in osteoarthritis and it is recognised that plain radiographs, MRI and arthroscopic findings do not universally correlate with pain or physical function.[54-56]

The most common method for assessing structural changes in knee osteoarthritis is plain radiography, graded using the Kellgren-Lawrence (K-L) classification.[57] Care has to be taken in interpreting plain

radiographic findings, as K-L grades have moderate but not strong correlations with other measures of structural change such as MRI measures of osteoarthritis or operative findings.[58-63]

The K-L classification is a widely accepted tool in osteoarthritis research and good reliability has been quoted in series in which the assessors were experienced in its use.[56, 61] However, it is based on a subjective assessment of structural changes and different authors often apply different criteria to define the boundaries between the grades, making comparisons across studies difficult.[64]

The boundary between Kellgren-Lawrence grade 2 and 3 is often difficult to define as the interpretation of 'possible' and 'definite' joint space narrowing can be very subjective.[65] However this is not so important when considering suitability for ACI, since the Nawaz study[23] showed that there was little difference in outcomes. The distinction between lower KL grades is also difficult is dependent on the interpretation of small osteophytes which can variably give a score of 0, 1 or 2 depending on the exact definitions used and the radiological technique.[64:#351]

The diagnosis of OA is often made based on the combination of symptoms and a K-L grade of 2 or more, despite evidence a that K-L grade of 1 ('doubtful osteophytes') has a high chance of progressing to 2 or more with time.[66:#353, 67]

The studies in this review have varied in terms of their reporting of the radiological assessment and definitions were not always clearly defined in the reports, and this may explain some of the variance in findings between studies. For example, relatively little detail is given in the Minas paper[68] on the radiological assessment and the Kellgren-Lawrence paper is not referenced, whereas the radiological grading is reported in detail by Nawaz.[23] A relatively high proportion of cases with KL grade 2 or above were reported by Knutsen[19], which may explain the poor results for ACI in this series in comparison to others.

As noted in the previous assessment report, it is possible that ACI may have a place in early OA with focal damage. Minas and colleagues [68] carried out ACI-P in 153 patients with an average age of 38, 38 and who had early OA, as shown radiologically by peripheral intra-articular osteophyte formation and/or joint space narrowing. Five years after ACI, 92% of patients had good function, and only 8% had had TKR. They included patients who had normal radiographs but evidence of kissing lesions.

Niemeyer and colleagues reported a case series of MACI (CartiGro cells and Chondro-Gide collagen membrane) in which some patients had early OA.[69] Their results were not as good as those in patients

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

In the SUMMIT trial [2], patients with Kellgren-Lawrence grade 3 or 4 OA were excluded, which implies that some patients with early OA (grade 2 has definite osteophytes and possible joint space narrowing) could have been included. However no details for such a sub-group are given in the results. In the TIG/ACT trial, patients with advanced OA (as defined by Radiographic Atlas OA grade 2 – 3) were excluded.

A systematic review of cartilage repair in early OA by de Windt et al[70] found evidence of benefit in those having various forms of ACI, ranging from ACI-P to MACI. Early OA was defined in different ways in the nine case series, and de Windt and colleagues described the studies as being of "generally low methodological quality". Nevertheless they reported that outcomes to 9 years were good, suggested that ACI in early OA might be used to postpone TKR, but recommended an RCT.

There may therefore be a place for ACI in early osteoarthritis, even if only to postpone TKR till patients are older, and some of the ICERs reported earlier are within the acceptable range. However, the evidence base is much weaker than for purely chondral lesions.

Defining OA is problematic. A big cartilage lesion with pain and some joint space loss could variably be defined as no, mild or moderate OA.

Age threshold for knee replacement

In our modelling we have assumed that TKR would not be performed for people with OA till age 55 or later. We used that age restriction because knee replacements do not last for ever, and replacing a replacement is more difficult, more expensive and less successful than the first replacement, and may not last as long.

With increasing longevity, it may no longer be the case that a knee replacement in someone over 60 is likely to last them all their days. Perhaps especially in women who live longer. However a TKR in a younger person with OA is very likely to need replacement. (This may not apply to people having KR because of inflammatory arthritis because their activity, and hence the stresses put upon the prosthesis, will often be limited by problems with other joints.)

The National Joint Registry 2015 report figure 3.16 shows that the probability of a first revision after TKR is higher in people who have replacements at younger ages. Those who have TKR under age 55, have a 12% probability of it being replaced by 11 years, which is more than double the risk after first TKR at older ages.

It is therefore a major decision to carry out TKR in people with OA under the age of 60 and very few are done. It should be noted that TKR is rarely an absolute necessity. The aim is to reduce pain, and that can be done in other ways, such as with analgesics or reducing activity.

It should also be borne in mind that TKR does not fully restore knee function. The TKR does not move like a normal knee, and younger active patients may find function on stairs and slopes disappointing.

ACI can restore normal function in younger patients. In patients who are older but too young for TKR, but who do not have generalised wear and tear, ACI may help bridge the gap to TKR even if the results are not as good as in younger patients with only an isolated chondral defect.

Conclusion

The evidence base has many deficiencies. One is that older studies tended to recruit patients who had had previous attempts at repair, and thse may give a misleadingly pessimistic picture of how ACI would perform if used as first procedure.

The evidence base for ACI is much better than for microfracture.

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Appendices

Appendix 1 Search strategy

The search strategy below was run in Ovid MEDLINE(R)1846 to May week 2 2005 and Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations May 15.

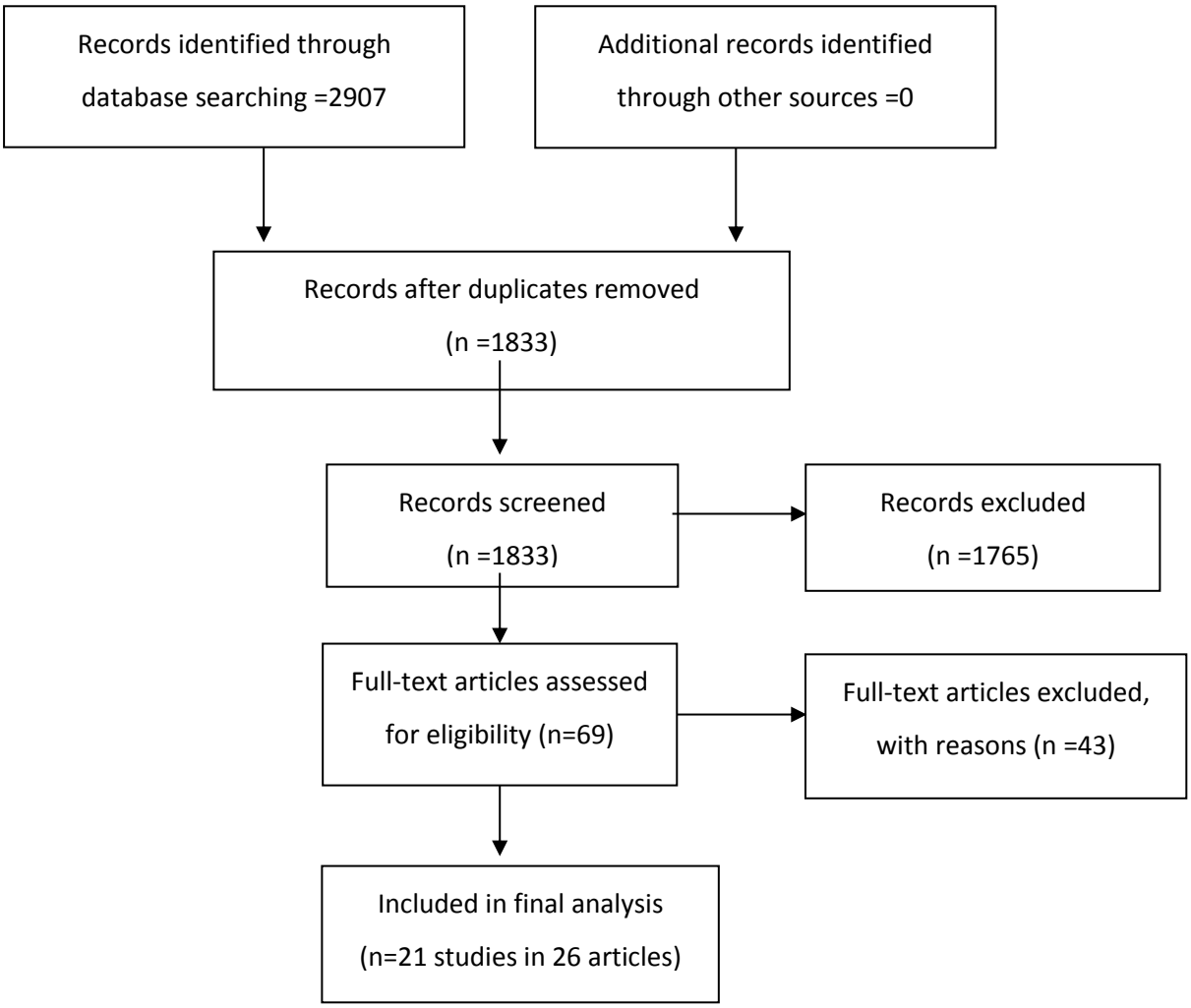
1. *Cartilage Diseases/su [Surgery]
2. *Arthroplasty, Subchondral/
3. *Cartilage, Articular/su [Surgery]
4. Chondrocytes/tr [Transplantation]
5. microfracture.tw.
6. (chondrocyte* adj4 (implant* or transplant* or matrix or characteri*)).tw.
7. (autologous adj3 (implant* or transplant* or chondrocyte* or cartilage)).tw.
8. (cartilage* adj2 (transplant* or implant*)).tw.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. knee.tw.
11. *Knee Injuries/su [Surgery]
12. 10 or 11
13. 9 and 12
14. limit 13 to yr="1997 -Current"
15. limit 14 to english language

The strategy below was run Ovid Embase 1974 to 2015 May 15

1. exp microfracture/
2. exp chondrocyte implantation/
3. *Cartilage Diseases/su [Surgery]
4. *Arthroplasty, Subchondral/
5. *Cartilage, Articular/su [Surgery]
6. microfracture.tw.
7. (chondrocyte* adj4 (implant* or transplant* or matrix or characteri*)).tw.
8. (autologous adj3 (implant* or transplant* or chondrocyte* or cartilage)).tw.
9. (cartilage* adj2 (transplant* or implant*)).tw.
10. knee.tw.
11. *Knee Injuries/su [Surgery]
12. 10 or 11
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
14. 12 and 13
15. limit 14 to (english language and yr="1997 -Current")

Flow Diagram

Figure 31 Flow diagram of searches



Appendix 2 Included studies – data extraction and quality assessment

Asik 2008[10]	**Data**
Title	The Microfracture Technique for the Treatment of Full-Thickness Articular Cartilage Lesions of the Knee: Midterm Results
Type of study	Cohort study (pre-post) Eligibility criteria reported
Quality of study NIH	Fair
Number of patients	90
Population	34.5 years (range, 20 to 58) 47.8% male Reason for injury not reported
Intervention	Microfracture
Duration of injury?	Not reported
Previous attempts at repair? (Don't count debridement and lavage – only previous microfracture, abrasion, drilling, ACI)	Not reported
Size of defect in cm^2 Depth or severity if given*	Mean not reported Reports N with <2cm and ≥2 cm (see subgroup results)
Duration of follow-up	1.5, 3, 6, 12 months and last visit. mean 68 months (range, 24 to 108 months)
Survival curve provided?	no
Results	
Lysholm score, mean (SD) [range]	Preop: 52.4 (6.2) [38-70] Last follow-up: 84.6 (7.8) [68-100] Change: 30.4 (4.2) p<0.0001
Tegner activity scale scores,	Preop: 2.6 (1.5) [2-5]

mean (SD) [range]	Last follow-up: 5.2 (1.3) [4-9] Change 2.6 (0.8) p<0.0001
Oxford knee questionnaire, mean (SD) [range]	Preop: 23.1 (4.8) [12-30] Last follow-up: 44.8 (5.7) [24-48] Change: 21.7 (3.8) p<0.0001
Subgroup data given?	
Lysholm score, mean (SD)	<u>age</u> <35 years, n=42, 36.2 (5.8) ≥35 years, n=48, 24.3 (6.1) p<0.001 <u>size of defect</u> <2 cm^2 n=68, 37.4 (5.9) ≥2 cm^2 n=22, 26.9 (4.7) p<0.001 <u>location of defect</u> weight-bearing surface n=42, 26.8 (5.3) non–weight-bearing surface, n=48, 37.3 (6.4) p<0.001 <u>body mass index</u> <25 kg/m^2 n=52, 38.2 (5.4) ≥25 kg/m^2 n=38, 26.2 (4.8) p<0.001
Tegner activity scale scores, mean (SD)	<u>age</u> <35 years, n=42, 2.6 (0.8) ≥35 years, n=48, 2.1 (0.4) p<0.001 <u>size of defect</u> <2 cm^2 n=68, 2.8 (0.6) ≥2 cm^2 n=22, 2.0 (0.4) p<0.001 <u>location of defect</u> weight-bearing surface n=42, 2.2 (0.5) non–weight-bearing surface, n=48, 2.6 (0.6) p<0.001 <u>body mass index</u> <25 kg/m^2 n=52, 2.8 (0.4) ≥25 kg/m^2 n=38, 2.0 (0.3) p<0.001
Oxford knee questionnaire, mean (SD)	<u>age</u> <35 years, n=42, 21.7 (3.4)

	≥35 years, n=48, 16.5 (2.8) p<0.001 size of defect <2 cm^2 n=68, 22.2 (3.6) ≥2 cm^2 n=22, 15.8 (2.8) p<0.001 location of defect weight-bearing surface n=42, 16.2 (2.7) non–weight-bearing surface, n=48, 23.2 (2.4) p<0.001 body mass index <25 kg/m^2 n=52, 22.8 (2.1) ≥25 kg/m^2 n=38, 16.3 (2.4) p<0.001
Losses to follow-up - % and reasons if given. How analysed? Assumed to have failed? (Don't expect details to be provided – case series will probably only include those not lost to F-U)	Excluded: 28 lost to regular follow-up 30 who had undergone a secondary surgical intervention after the index operation (16 anterior cruciate ligament [ACL] ruptures, 13 meniscus ruptures, and 1 posterior cruciate ligament rupture). 98 because an ACL rupture, meniscal lesion, patellofemoral problems, plica lesion, other location of defect, or more than 1 location of defect was observed at index operation.
Any costs given?	No
Survival curve	No

Quality Assessment Tool for Case Series Studies NIH

Criteria	**Yes**	**No**	**Other (CD, NR, NA)***
1. Was the study question or objective clearly stated?	y		
2. Was the study population clearly and fully described, including a case definition?	y		
3. Were the cases consecutive?			CD
4. Were the subjects comparable?	y		
5. Was the intervention clearly described?	y		
6. Were the outcome measures clearly defined, valid, reliable, and	y		

implemented consistently across all study participants?			
7. Was the length of follow-up adequate?	y		
8. Were the statistical methods well-described?	y		
9. Were the results well-described?	y		
Quality Rating Fair			

*CD, cannot determine; NA, not applicable; NR, not reported

Bentley 2012[11]	**Data**
Title	Minimum ten-year results of a prospective randomised study of autologous chondrocyte implantation versus mosaicplasty for symptomatic articular cartilage lesions of the knee
Type of study	Long term results of Bentley 2003 RCT of MF versus mosaicplasty so only MF arm used here
Quality of study	Uncertain risk of bias (Cochrane risk of bias tool)
Number of patients	ACI: 58 Mosaicplasty: 42 (data not extracted)
Population	Total group mean 31.3 years (range 16 – 49) ACI: 30.9 years (16 to 49) 58% male Reason for injury? ACI: Trauma 24 (41%); Osteochondritis dissecans 14 (24%); Chondromalacia patellae 12 (21%); Other/Unknown: 8 (14%)
Intervention	ACI-P or ACI-C
Duration of injury?	Mean 7.2 years (range 9 months to 20 years)
Previous attempts at repair? (Don't count debridement and lavage – only previous microfracture, abrasion, drilling, ACI)	94 (94%) had previous surgery (no details by study arm). Number of previous repairs, mean 1.5 (range 0 to 4). included microfracture, abrasion, debridement, drilling, and carbon-fibre matrix support prostheses
Size of defect in cm^2 Depth or severity if given*	ACI 44.1 cm^2 (10 to 105)
Duration of follow-up	Minimum 10 years (range 10-12)
Survival curve provided?	Yes
Results	
Failure	ACI 10/58 (17%) Defined as a clinically poor result with arthroscopic evidence of failure of the graft, or revision surgery to the defect of any kind
modified Cincinnati rating system Graded as: excellent (> 80 points), good (55 to 79)	ACI: N=48 (10 failures excluded) Excellent 28 Good 7 Fair 6 Poor 2

fair (30 to 54) poor (< 30 points)	Excellent or good seen as significant improvement, fair as marginally better or unchanged, poor as worse.
Stanmore-Bentley functional rating system Function and pain measure, five-point scale of pain related to function (0 = no pain with any activity, 4 = pain at rest and severe pain with activity).	ACI: 0: 7 1: 23 2: 3 3: 6 4: 4
Subgroup data	
Kaplan-Meier estimates (SE) of percent failure rates at 5 years according to pre-operative factors	Age, p=0.028 < 26 (n= 16) 0 (-) 26 to 35 (n= 25) 8 (5) > 35 (n= 17) 12 (8) Gender, p=0.87 Male (n= 33) 6 (4) Female (n= 25) 8 (5) Cause, p=0.31 chondromalacia patellae (n= 11) 19 (12) osteochondritis dissecans (n= 11) 0 (0) Trauma (n= 29) 7 (5) Other/Unknown (n= 7) 0 (-) Site, p=0.81 lateral femoral condyle (n= 11) 9 (9) medial femoral condyle (n= 24) 8 (6) Patella (n= 20) 5 (5) Other/Unknown (n= 3) 0 (-)
Losses to follow-up - % and reasons if given. How analysed? Assumed to have failed? (Don't expect details to be provided – case series will probably only include those not lost to F-U)	ACI 5 (8.6%) Patients who were lost to follow-up were included until last review and then withdrawn from the study.
Any costs given?	no
Only for papers with survival curves	
Is curve Kaplan-Meier? If not, what is it?	Yes
Risk table attached?	No
Total events reported?	No
Hazard ratios, p value and/or 95% CI, and whether adjusted or not.	No

*usually not given since repairs only in people with full thickness defect – i.e. cartilage defect down to bone.

Cochrane Risk of Bias

Bias	**Author judgement**	**Support for judgement**

Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Unclear risk	Sequential envelopes, unclear if opaque
Blinding of participants and personnel (performance bias)	Unclear risk	No details
Blinding of outcome assessment (detection bias)	Unclear risk	No details
Incomplete outcome data (attrition bias)	Unclear risk	Some missing data for subjective outcomes for one study arm (not relevant to the review though)
Selective reporting (reporting bias)	Unclear risk	No information to judge
Other bias	Low risk	

Beris 2012[12]	**Data**
Title	Treatment of Full-Thickness Chondral defects of the Knee With Autologous Chondrocyte Implantation: A Functional Evaluation With Long-Term Follow-up
Type of study	Case series
Quality of study NIH	Fair
Number of patients	42 (45 knees)
Population	Mean age 28.9 (range 12-47) years 69% male Reason for injury? - Trauma (38/45 knees) - Osteochondritis dissecans (7/45 knees)
Intervention	ACI-P
Duration of injury?	28 months
Previous attempts at repair?	Not reported
Size of defect in cm^2 Depth or severity if given*	Mean 5.33cm^2 (range 1.8 – 12cm^2) All had isolated moderate to large full-thickness (Outerbridge grade III or IV) chondral defects
Duration of follow-up	Mean 96 months (range 62-144) Evaluation at 6, 12, 24, 48 months and annually thereafter
Survival curve provided?	No
Results	
Lysholm score, median	Preop: 56.0 Last follow-up: 89.0 $p<0.05$
IKDC	Preop: 45 Last follow-up: 69 $p<0.05$
Tegner activity score	Preop: 5.5 Last follow-up: 6.5 $p<0.05$
ICRS	Preop: 3.8

	Last follow-up: 2.8 p<0.05
Stanmore functional rating score	Preop: 3.06 Last follow-up: 0.94
Pain VAS	Preop: 7.33 Last follow-up: 2 p<0.05 Doesn't appear to be a validated scale.
Subgroup data given?	none
Losses to follow-up - % and reasons if given. How analysed? Assumed to have failed? (Don't expect details to be provided – case series will probably only include those not lost to F-U)	Not applicable
Any costs given?	None
Survival curve?	No

Quality Assessment Tool for Case Series Studies NIH

Criteria	**Yes**	**No**	**Other (CD, NR, NA)***
1. Was the study question or objective clearly stated?	y		
2. Was the study population clearly and fully described, including a case definition?	y		
3. Were the cases consecutive?		N	
4. Were the subjects comparable?	y		
5. Was the intervention clearly described?	Y		
6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?			CD
7. Was the length of follow-up adequate?	Y		
8. Were the statistical methods well-described?	Y		
9. Were the results well-described?		N	
Quality Rating) Fair			

Additional Comments : Selective reporting of study results Reports median for Lysholm score, mean or median not stated for other outcomes. No measure of variance.

*CD, cannot determine; NA, not applicable; NR, not reported

Bhosale 2009[13]	**Data**
Title	Midterm to Long-Term Longitudinal Outcome of Autologous Chondrocyte Implantation in the Knee Joint
Type of study	Cohort study
Quality of study NIH	Poor
Number of patients	80
Population	Mean 34.6 (SD 9.1) years 78.8% male Reason for injury not reported
Intervention	ACI-P
Duration of injury?	Not reported
Previous attempts at repair? (Don't count debridement and lavage – only previous microfracture, abrasion, drilling, ACI)	Previous repair (not defined) 70/80 (87.5%) had median of 1 (Interquartile range [IQR] 1-2) repairs)
Size of defect in cm^2 Depth or severity if given*	Median defect area 4.1 cm^2 (IQR, 3.0-6.0) maximum size 20 cm^2
Duration of follow-up	Mean 5 years (range, 2.7-9.3)
Survival curve provided?	No
Results	
modified Lysholm score, median IQR	Preop: 54 (IQR 35.5-68.5) 1 year: 78 (IQR, 52-87) median increase of 24 points.
Subgroup data given?	Age Gender Defect size Defect location (lateral femoral condyle; medial femoral condyle; multiple defects; trochlea; other) Previous procedures Baseline Lysholm score Regression analysis as potential predictors for change in Lysholm score. Results not extracted.
Losses to follow-up - % and reasons if given. How analysed? Assumed to have failed? (Don't expect details to be provided – case series will probably only include those not lost to F-U)	Not applicable
Any costs given?	none

Survival curve?	No

*usually not given since repairs only in people with full thickness defect – i.e. cartilage defect down to bone.

** http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

Quality Assessment Tool for Case Series Studies NIH

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the study question or objective clearly stated?	Y		
2. Was the study population clearly and fully described, including a case definition?	Y		
3. Were the cases consecutive?	y		
4. Were the subjects comparable?	y		
5. Was the intervention clearly described?	Y		
6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?	Y		
7. Was the length of follow-up adequate?	Y		
8. Were the statistical methods well-described?	Y		
9. Were the results well-described?		N	
Quality Rating Fair			
Additional Comments: Long term data measured but not reported			

*CD, cannot determine; NA, not applicable; NR, not reported

Biant 2014[14]	**Data**
Title	Long-term Results of Autologous Chondrocyte Implantation in the Knee for Chronic Chrondral and Osteochondral Defects
Type of study	Case series

Quality of study	Good
Number of patients	104
Population	mean age (range): 30.2 years (15-49 years) 52.9% male Reason for injury? - Trauma: 55 (53%) - Osteochondritis dissecans: 17 (16%) - Chondromalacia patellae: 23 (22%) - Childhood osteomyelitis: 2 (2%) - Other/unknown: 7 (7%)
Intervention	ACI-P
Duration of injury?	Mean 7.8 years
Previous attempts at repair? (Don't count debridement and lavage – only previous microfracture, abrasion, drilling, ACI)	- Previous repair (microfracture, drilling, mosaicplasty, carbon fiber matrix-support prosthesis): 73 (70%) had ≥1 previous operation; - 31 (29.8%) had previous arthroscopic surgery and arthroscopic debridement: - Number of previous repairs: mean 1.3 (range 0-5)
Size of defect in cm^2 Depth or severity if given*	4.78cm^2 (range, 1.2-25cm^2).
Duration of follow-up	Minimum of 10 years (range 10-12 years) Mean 5.7 years graft failure
Survival curve provided?	Yes
Results	
Graft failure	27 (26%) All occurred within 8 years Defn: patients who underwent revision surgery of any kind (thereby altering or removing the original graft) or arthroplasty
Pain, VAS, 10 point scale	Preop: 6 Change to last follow-up: -8.3 (95% CI -10.8, -5.8)
Modified Cincinnati knee score excellent (>80 points), good (55-79 points), fair (30-54 points), poor (<30 points).	Preop: not reported Last follow-up (intact graft, n=73): 78 (range, 10-100) Change: 53 (95% CI 34, 71) Excellent: 46 (63%) Good: 18 (24.7%) Fair: 6 (8.2%) Poor: 3 (4.1%)
Stanmore/Bentley functional rating system	Preop: not reported. Assume change score is for patients with an intact graft (n=73) Change to last follow-up: -2.6 (95% CI -3.7, -1.5) Score (n=73?), n (%) 0: 14 (19.2%) 1: 38 (52.1%) 2: 8 (11%) 3: 8 (11%) 4: 5 (6.8%)
Satisfaction Patients asked by an independent interviewer if they were satisfied with	98/100 (98%)

their ACI surgery and whether they would consider undergoing it again if the same symptoms arose in the other knee	
Complications	3 (2.9%) 2 (1.9%) manipulation under anesthesia within 8 weeks of surgery because of early postoperative stiffness, 1 (0.96%) deep vein thrombosis
Subgroup data given?	No prior cartilage surgery, n=32 Preop modified Cincinnati knee score: mean 49 (range, 18-94). Last follow-up mean 71 (range, 10-100) Preop Stanmore/Bentley score mean 3 (range, 1-4) Last follow-up mean 1.5 (range, 0-4) Preop mean VAS score 7 (range, 1-10) Last follow-up: mean 3.5 (range, 0-10). Graft failures 6/32 (18.7%)
4 were lost to follow-up but ITT n used here for proportion	Prior cartilage repair surgery, n=72. States 73 earlier in report Preop modified Cincinnati knee score mean 42 (range, 12-82) Last follow-up: mean 65 (range, 10-100) Preop Stanmore/Bentley score mean 3 (range, 0-4) Last follow-up: 2 (range, 0-4) Preop mean VAS score was 5.5 (range, 0.5-10) Last follow-up: mean 3.5 (range, 0-10) Graft failures: 21/72 (29.2%)
Patellar lesions, n=36	N=36 Preop mean modified Cincinnati knee score: 40 (range, 14-73) Last follow up (n=27): 79 (range, 48-100) Excellent: 17 (63%) Good: 8 (30%) Fair: 2 (7%) Preop mean Stanmore/Bentley score 3 (range, 2-4) Last follow-up (n=27): 1.3 (range, 0-4) Preop mean VAS score 6.4 (range, 2.5-10). Last follow-up (n=27): 2 (range, 0-8) Graft failure: 9 (25%) The mean time to failure 5.8 years (range, 1-8 years).
Losses to follow-up - % and reasons if given. How analysed? Assumed to have failed?	4 (3.8%)

Any costs given?	No
Survival curve?	No

*usually not given since repairs only in people with full thickness defect – i.e. cartilage defect down to bone.

Quality Assessment Tool for Case Series Studies NIH

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the study question or objective clearly stated?	Y		
2. Was the study population clearly and fully described, including a case definition?	Y		
3. Were the cases consecutive?	y		
4. Were the subjects comparable?	y		
5. Was the intervention clearly described?	Y		
6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?	Y		
7. Was the length of follow-up adequate?	Y		
8. Were the statistical methods well-described?	Y		
9. Were the results well-described?	Y		
Quality Rating Good			

*CD, cannot determine; NA, not applicable; NR, not reported

Browne 2005[15]	**Data**
Title	Clinical outcome of autologous chrondrocyte implantation at 5 years in US subjects.
Type of study	Case series Prospective registry from 40 centres
Quality of study NIH	Poor
Number of patients	100
Population	mean 37.0 (SD 9.1), range 14-55 years 65% male Reason for injury? - Acute injury: 58/100 (58%)
Intervention	ACI-P
Duration of injury?	Not reported
Previous attempts at	- At least 1 surgical procedure: 78/100 (78%)

repair? (Don't count debridement and lavage – only previous microfracture, abrasion, drilling, ACI)	- At least 1 cartilage repair procedure: 70/100 (70%) - Abrasian/drilling/microfracture: 36/100 (36%) - Fragment reattachment/removal: 1/100 (1%) - Osteochondral allograft/autograft: 1/100 (1%) - ACI: 1/100 (1%) - Meniscus repair/meniscectomy: 32/100 (32%) - Ligament repair/reconstruction: 14/100 (14%) - Patella alignment: 1/100 (1%) - Other: 4/100 (4%)
Size of defect in cm^2 Depth or severity if given*	Mean 4.9cm^2 (SD 3.8, range 0.84-23.54) <2.0cm^2: 15/100 (15%) 2.0-<4.0cm^2: 38/100 (38%) 4.0-<6.0cm^2: 17/100 (17%) ≥6.0cm^2: 30/100 (30%) Multiple defects: 15/100 (15%)
Duration of follow-up	5 years
Survival curve provided?	no
Results	
Overall condition score, mean (SD), n=87 Modified Cincinnati Knee Rating system	Preop: 3.2 (1.5) 5 year follow-up: 5.8 (2.8) Change: 2.6 (3.2); p<0.0001 (95% CI 1.9,3.2)
Pain mean (SD), n=86 Patient rated measure (6 point scale 0-10), unlikely validated.	Preop: 3.1 (2.2) 5 year follow-up: 5.5 (3.2) Change: 2.3 (3.7); p<0.0001 (95% CI 1.5,3.1) Preop: 4.1 (2.7) 5 year follow-up: 6.1 (3.1) Change: 2.0 (3.8); p<0.0001 (95% CI 1.2,2.8) Swelling mean (SD), n=85
Proportion in response sets	Improved: 62/100 (62%) No change: 6/100 (6%) Worsened: 19/100 (19%) Definitions not provided; states 'additional examination'
Failure Cases in which a patient needed an operation after autologous chondrocyte implantation that necessitated the removal of the graft, confirmed a loss of defect fill, or violated the subchondral bone (eg abrasion chondroplasty,	13/100 (13%)

microfracture, drilling, unicompartmental knee replacement, total knee replacement).	
Complications	Joint infections, n=0 Arterial injuries, n=0 Nerve injuries, n=0 Deep Vein Thrombosis, n=1 Reflex sympathetic dystrophy, n=1 Closed manipulation under anaesthesia, n=2
Subgroup data given? Modified Cincinnati Knee Rating system Overall condition, change from baseline	Men (n=65) vs women (n=35): 2.4 vs 2.8 Concurrent procedures (n=21) vs no concurrent procedures (n=79): 2.5 vs 2.6
Overall condition	Patients rated as improved, n=62 Preop: 3.0 (1.4) 5 year follow-up: 7.1 (2.2) Change: 4.1 (2.2); p<0.0001 (95% CI 3.6,4.7)
Losses to follow-up - % and reasons if given. How analysed? Assumed to have failed?	Unable to collect 5-year follow-up data on 13 participants. Numbers reporting outcomes varied from 62-87
Any costs given?	No
Survival curve?	No

Quality Assessment Tool for Case Series Studies NIH

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the study question or objective clearly stated?	Y		
2. Was the study population clearly and fully described, including a case definition?	Y		
3. Were the cases consecutive?	Y		
4. Were the subjects comparable?	y		
5. Was the intervention clearly described?	Y		
6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?		N	

7. Was the length of follow-up adequate?	Y		
8. Were the statistical methods well-described?	Y		
9. Were the results well-described?		N	
Quality Rating Poor			
Additional Comments (If POOR, please state why): Proportion 'improved' and 'worsened' not defined.			

*CD, cannot determine; NA, not applicable; NR, not reported

Gomoll 2014[16]	**Data**
Title	Autologous Chondrocyte Implantation in the Patella: A multicentre experience
Type of study	Case series. Retrospective analysis but based on a prospective patient registry from 4 centres specialising in cartilage repair. All 4 surgeons had extensive experience
Quality of study	Poor
Number of patients	110 Additional 23 were lost to follow-up (follow-up rate 83%).
Population	Age – mean 33 (SD10.1) years (range 15-55) 41.8 % male No bilateral ACI included All patients with ACI for patellar defects (including trochlear graft) with at least 4 years follow-up were included. Defects outside the patellofemoral compartment were excluded. Text discusses differences in population by centres (not data extracted)
Intervention	ACI-P (procedure described by Minas el al 1999)
Duration of injury?	Reported symptoms for mean of 3 years (SD 35 months), range 2-144 months
Previous attempts at repair?	Mean of 1.2 previous surgery (range, 0-12; SD, 1.7) Most common prior procedures were chondroplasty and lateral release.
Size of defect in cm^2 Depth or severity if given*	Mean 5.4 cm^2 (SD 2.7), (range, 1-13.2). 30 (27%) had bipolar disease with an additional trochlear defect, mean size of 4.5 cm^2 (SD 2.8), (range, 1-13 cm^2). 12 distal (11%; type I), 3 lateral (3%; type II), 16 medial (15%; type III), and 79 central/panpatellar defects (72%; type IV). By Pidoriano/Fulkerson classification. 82 (75%) of patellar defects and 26 (87%) of trochlear defects were circumferentially shouldered by healthy cartilage (contained).
Duration of follow-up	mean of 90 (SD 31.7) months, (range 48-192) States data collected yearly intervals. Patient reported outcomes analysed at latest follow-up
Survival curve provided?	No

Results	Measured at latest follow-up
SF-12 Short-form 12 (QoL)	Physical subscale, n=89 (81%) Baseline: 38.6 Last follow-up 44.1 (p = 0.001) Mental subscale, n=89 (81%) Baseline: 49.7 Last follow-up: 53.5 (p = 0.1).
KSS	Knee, n=44 (40%) Baseline: 61.8 Last follow-up: 85.2 (p<0.001) Function n=44 (40%) Baseline: 58.5 Last follow up: 72.7 (p<0.0001).
IKDC	N=65 (60%) Baseline: 40.2 Last follow up: 69.4 (p<0.0001) 86% and 74% of patients demonstrated more than 10 and 20 points of improvement, respectively (considered to exceed the minimal clinically important difference)
modified Cincinnati Rating Scale, range 2-10	N=85 (78%) Baseline: 3.2 Last follow up: 6.2 (p<0.0001).
WOMAC	N=44 (40%) Baseline: 50.4 Last follow up: 28.6 (p<0.0001). 75% of patients exceeded a commonly accepted threshold for MCIDs, with more than a 26% improvement in WOMAC from baseline
Satisfaction with procedure Measure used not reported	N=93 (84.5%) 84% felt improvement at the time of final follow-up; 86% rated their knee function as good or excellent; 92% would choose to undergo ACI again
Treatment failure	9/110 (8.2%). If diagnosed by MRI and/or athroscopy with structural failure of the ACI graft in conjunction with pain requiring revision surgery
Subgroup data given?	p-values only given, data not extracted. States that none of the differences among subgroups reached statistical significance: polarity (bi- vs unipolar), containment (contained vs uncontained; patellar defects only), concomitant tibial tuberosity transfer (yes vs no), patellar defect location (lateral, medial, panpatellar), defect size (<4cm^2 vs. >4cm^2) sex (male vs female)
Losses to follow-up - % and reasons if given.	Not applicable (only those not lost to follow-up were included) Note that questionnaires were added as they became available and validated, and start date varied between institutions. Therefore not all patients answered the same battery of questionnaires.
Any costs given?	none
Survival curve?	No

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Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the study question or objective clearly stated?	y		
2. Was the study population clearly and fully described, including a case definition?	y		
3. Were the cases consecutive?		n	
4. Were the subjects comparable?	y		
5. Was the intervention clearly described?	y		
6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?	y		
7. Was the length of follow-up adequate?	y		
8. Were the statistical methods well-described?	y		
9. Were the results well-described?		N	
Quality Rating (Good, Fair, or Poor)			
Additional Comments (If POOR, please state why): Measures of variance not reported			

*CD, cannot determine; NA, not applicable; NR, not reported

Jungmann 2012[17]	**Data**
Title	Autologous Chondrocyte Implantation for Treatment of Cartilage Defects of the Knee
Type of study	Case series Retrospective analysis of prospective database. Described in paper as a cohort study, level 3 evidence
Quality of study	Good
Number of patients	413
Population	Age 34.9 (SD 9.0) years 57.4% male Origins of the cartilage defect:

	Traumatic 7.0% Degenerative 52.0% Protracted traumatic-degenerative28.3% Previous osteochondritis dissecans or flake fracture (12.6%).
Intervention	ACI-P (n=109) ACI-C (n=235) MACI (n=69) CellGenix (Freiburg, Germany) for cell suspensions (periosteum patch–covered ACI and Chondro-Gide–covered ACI) or BioTissue Technologies (Freiburg, Germany) for Bio- Seed-C (matrix associated) procedure.
Duration of injury?	Not reported
Previous attempts at repair? (Don't count debridement and lavage – only previous microfracture, abrasion, drilling, ACI)	No previous knee surgery: 29.8% Microfracture: 18.6% Pridie drilling: 7.3% ACI: 4.2% Abrasion arthroplasty/ Debridement: 3.1% Mosaic plasty (OATS): 1.9% Autologous spongiosa graft: 1.7% Retrograde drilling: 0.72%
Size of defect in cm^2 Depth or severity if given*	5.6 (SD 3.0)
Duration of follow-up	2 years to 11.8 years. Follow-up cut-off was at 5 years. 62.5% had a follow-up at 5 years.
Survival curve provided?	Yes
Results	
Revision surgery (treatment failure), n (%)	Treatment failure, represented by need for revision surgery, indicated by: - persistent pain at the operated knee joint; - significant loss of function of the operated knee joint; and - clinical findings and/or MRI revealed compatibly pathologic changes to confirm symptoms, such as MRI evidence of graft delamination, hypertrophy, severely abnormal signal, insufficient fusion with adjacent cartilage, or secondary transplant defects. 88/413 (21.3%) ACI-P: 34/109 (31.2) ACI-C: 43/235 (18.3) MACI: 11/69 (15.9) Periosteum patch–covered technique (P = 0.031; odds ratio, 2.4 [BioSeed-C] vs 2.0 [Chondro-Gide]) increased the risk for the need of reintervention
Time to revision surgery, mean (SD) years	ACI-P: 1.7 (1.2) ACI-C: 1.7 (1.1) MACI: 2.4 (1.2) P=ns
Subgroup data	Age, years

Treatment failure (revision), prognostic factors n % Defects related to a trauma within the past 6 months before surgical treatment were considered ‘‘traumatic,’’ while those associated with a traumatic incident more than 6 months before surgical treatment were considered ‘‘posttraumatic.’’ Degenerative’’ defects were considered those cases in which no trauma could be evaluated.	<30: 24/123 (19.5) 30-39: 39/179 (21.8) ≥40: 25/111 (22.5) BMI <25: 55/232 (23.7) 25-29: 25/149 (16.8) ≥ 30: 8/32 (25.0) Number of defects 1: 74/340 (21.8) >1: 14/73 (19.2) Defect size, cm^3 <3: 12/44 (27.3) ≥3: 76/369 (20.6) Cause Degenerative: 43/215 (20.0) Protracted traumatic-degenerative:26/117 (22.2) Osteochondritis dissecans, flake fracture: 11/52 (21.2) Trauma: 8/29 (27.6) Gender Male: 41/237 (17.3) Female: 47/176 (26.7) Location Multiple: 13/68 (19.1) Patella: 26/111 (23.4) Medial femoral condyle: 36/168 (21.4) Lateral femoral condyle: 3/37 (24.3) Trochlea: 4/29 (13.8) Nicotine No: 59/298 (19.8) Yes: 29/115 (25.2) Parallel treatment Without: 67/306 (21.9) With: 21/107 (19.6) Previous surgery No: 17/123 (13.8) 1: 41/223 (20.2) >1: 26/67 (38.8) Previous treatment No: 54/289 (18.7) Bone marrow stimulation: 28/94 (29.8) Previous transplantation: 5/23 (21.7) Other: 1/7 (14.3) Female gender (P = 0.015; odds ratio, 1.7), more than one previous surgery (P <0.001; odds ratio, 4.0), and previous BMS (P = 0.017; odds ratio, 1.9), increased the risk for the need of reintervention.
Losses to follow-up - % and reasons if given. How analysed? Assumed to have failed? (Don’t expect details to be provided – case series will probably only include	Not applicable

those not lost to F-U)	
Any costs given?	No
Survival curve?	no

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Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the study question or objective clearly stated?	y		
2. Was the study population clearly and fully described, including a case definition?	y		
3. Were the cases consecutive?		No	
4. Were the subjects comparable?	y		
5. Was the intervention clearly described?	y		
6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?	y		
7. Was the length of follow-up adequate?	y		
8. Were the statistical methods well-described?	y		
9. Were the results well-described?	y		
Quality Rating Good			

*CD, cannot determine; NA, not applicable; NR, not reported

Knutsen 2007[19]	**Data**
Title	A Randomized Trial Comparing Autologous Chondrocyte Implantation with Microfracture
Type of study	RCT
Quality of study	Uncertain risk of bias
Number of patients	Total 80 ACI 40 Microfracture 40
Population	Reason for injury Trauma 65% Osteochondritis dissecans 28% Unknown 7% Baseline characteristics available in online supplement – unable to

	access
Intervention	ACI-P Microfracture
Duration of injury?	36 months
Previous attempts at repair? (Don't count debridement and lavage – only previous microfracture, abrasion, drilling, ACI)	74 (93%) had previous knee surgery, including anterior cruciate ligament reconstruction (15), meniscal surgery (14), arthroscopic lavage and debridement (29), Pridie drilling (3), operations for osteochondritis dissecans such as drilling or fixation of a fragment (13).
Size of defect in cm^2 Depth or severity if given*	No included defects were deeper than 10 mm.
Duration of follow-up	5 years
Survival curve provided?	Yes
Results	
Failures Operation considered to have failed if patient needed reoperation because of symptoms due to a lack of healing of the treated defect. The need for shaving or trimming of a lesion was not defined as a failure.	ACI: 9/40 (23%) Microfracture 9/40 (23%) Failures occurred at a mean of 26.2 months after ACI and 37.8 months after microfracture (p = 0.101).
Median Lysholm score (assume range)	ACI Estimated from figure Baseline 62 (25-90) 5 year 78 (21-100) Microfracture Baseline 58 (12-95) 5 year 80 (37-100) Difference between groups p=0.227 after adjustment for pre-treatment values
VAS pain scale, median (assume range)	Estimated from figure ACI Baseline 52 (2-100) 5 year 26 (0-100) Microfracture Baseline 52 (18-83) 5 year 26 (0-86) Difference between groups p=0.278 after adjustment for pre-treatment values
SF-36 physical component score (PCS), median (assume range)	Estimated from figure ACI Baseline 42 (26-58) 5 year 48 (20-65) Microfracture Baseline 38 (20-56)

	5 year 48 (12-68) Difference between groups p=0.054 after adjustment for pre-treatment values
Proportion compared with baseline	Less pain: 72% Improvement in Lysholm score: 80% Improvement in SF-36 PCS: 72%
Mean Tegner score	ACI Baseline: 3.28 5 years: 4.05, p=0.007 Microfracture Baseline: 3.16 5 years: 4.36, p=0.002 Difference between groups p=0.323 after adjustment for pre-treatment values
Subgroup data	
Number of failures by 5 years Grade 1 = predominantly hyaline tissue, grade 2 = fibrocartilagehyaline mixture, grade 3 = fibrocartilage, and grade 4 = inadequate biopsy or no repair tissue (predominantly bone). None of the patients with a failure had the best-quality cartilage (p = 0.001).	Histological grade (no. of knees):no of failures 1: (n=10) 0 2: (n= 16) 3 3 (n=29) 6 4 (n=12) 3
	Younger patients (less than thirty years old) had a better clinical outcome than did older patients (p = 0.013), regardless of their treatment group. Data not presented, unclear if subgroup defined apriori
Losses to follow-up - % and reasons if given. How analysed? Assumed to have failed? (Don't expect details to be provided – case series will probably only include those not lost to F-U)	No losses to follow-up. The patients with a failure remained in the study, with their last recorded clinical follow-up scores before the failure considered to be their final clinical score.
Any costs given?	No
Survival curve?	No

*usually not given since repairs only in people with full thickness defect – i.e. cartilage defect down to bone.

Bias	**Author judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported

Blinding of participants and personnel (performance bias)	Unclear risk	Not reported
Blinding of outcome assessment (detection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Low risk	No losses to follow-up
Selective reporting (reporting bias)	Unclear risk	
Other bias	Low risk	

Krych 2012[18]	**Data**
Title	Activity Levels Are Higher After Osteochondral Autograft Transfer Mosaicplasty Than After Microfracture for Articular Cartilage Defects of the Knee
Type of study	Case series (retrospective) Only MF data extracted
Quality of study	 Good
Number of patients	48 with full depth lesions Analysed at 1, 2, 3 and 5 years follow up; mean follow up 4.4 years (range 2 – 10)
Population	Age at MF, mean 32.5 (range 15-46) years Male/female: 32:16 Lesion Mean Size (cm^2) 2.55 (range 1.00-6.25) BMI 25.5 kg/m^2 (range, 21 to 31 kg/m^2) Defect locations Medial femoral condyle n 27 Lateral femoral condyle n 16 Trochlea n 5
Intervention	Microfracture
Duration of injury?	Not reported
Previous attempts at repair?	None
Size of defect in cm^2 Depth or severity if given*	Mean 2.55 cm^2 (range, 1.00 to 6.25 cm^2) Full depth lesions
Duration of follow-up	Mean follow up 4.4 years (range 2 – 10)
Survival curve provided?	No
Results	
Definitions of success and failure	Not reported
SF 36 Physical component mean (SD) SD 10 read from graph	Preop 40.5 (10) Yr1 47.9 (10) Yr2 50.8 (10) Yr3 52.6 (10) Yr5 52.0 (10)
The Knee Outcome Survey activities of daily living score mean (SD) SD read from graph.	Preop 64.1 (16) Yr1 78.7 (19) Yr2 79.1 (16) Yr3 86.6 (13.4) Yr5 84.4 (15.6)
SD read from graph.	Preop 49.7 (16)

	Yr1 65.4 (16) Yr2 69.2 (24) Yr3 69.2 (25) Yr5 84.4 (26)
Marx Activity Rating Scale score, mean (SD)	Preop 7.3 (5.4) Yr1 4.11 (1.05) Yr2 3.71 (1.64) Yr3 2.91 (2.12) Yr5 2.89 (2.5)
Subgroup data	None reported
Losses to follow-up - % and reasons if given. How analysed? Assumed to have failed? (Don't expect details to be provided – case series will probably only include those not lost to F-U)	Not reported
Any costs given?	No
Survival curve?	No

*usually not given since repairs only in people with full thickness defect – i.e. cartilage defect down to bone.

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Criteria	**Yes**	**No**	**Other (CD, NR, NA)***
1. Was the study question or objective clearly stated?	y		
2. Was the study population clearly and fully described, including a case definition?	y		
3. Were the cases consecutive?			CD
4. Were the subjects comparable			NA
5. Was the intervention clearly described?	y		
6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?	y		
7. Was the length of follow-up adequate?	y		
8. Were the statistical methods well-described?	y		
9. Were the results well-described?	y		

Quality Rating Good

*CD, cannot determine; NA, not applicable; NR, not reported

Moseley 2010[22]	
Title	**Long-Term Durability of Autologous Chondrocyte Implantation; A Multicenter, Observational Study in US Patients**
Type of study	Case series
Quality of study	Fair to good
Number of patients	72
Population	N 72 Mean follow up (years) 10.9 SD 1.1 Mean age (years) 37.0 ± 9.27 range 14-53 Male (%) 61 % with single defect 60/72 % with multiple defects 12/72 BMI Mean ± SD 27.2 range 13.2-42.4 Defect size : Total surface area, cm^2: Mean 5.2 Range 0.4-23.5 Defect sites (total defects=84) Medial Femoral % 72 Lateral Femoral % 18 Trochlea % 10
Intervention	Carticel (Genzyme) ACP ACP received on or before 1996; 2,044 of 2194 excluded because ACI treatment occurred after December 31, 1996
Duration of injury?	Not reported; 47/62 had acute onset of injury
Previous attempts at repair? (Don't count debridement and lavage – only previous microfracture, abrasion, drilling, ACI)	Previous intervention (in previous 5 years) % At least 1 surgical procedure 74% At least 1 cartilage repair procedure 68% Abrasion/drilling/microfracture (MST) 36% Meniscus repair/meniscectomy 28%
Size of defect in cm^2 Depth or severity if given*	Size (cm^2) 5.2 Range 0.4-23.5. Full-thickness defects.
Duration of follow-up	6 to 10 years
Survival curve provided?	Yes
Results	
Failure	Failure defined as : patient needed an operation after ACI that necessitated removal of the graft, confirmed a loss of defect fill, or violated the subchondral bone (eg, abrasion chondroplasty, microfracture, drilling, uni-compartmental knee replacement, total knee. Failures =12/72 18 patients who did not meet the definition of failure had operations for: *presence of fibrotic tissue (4), periosteal flap complications (4), graft hypertrophy (3), adhesions (3), loose body (2), synovitis (2), & maltracking (2).*
Overall condition score (OCS): a 1 to 10	Improved at 1-5 yrs & at 6-10 yrs N=47 Improved at 1-5 yrs not at 6-10 yrs N=7

VAS with status allocated to scores of 2, 4, 6, 8, 10 defined respectively as follows: Poor : *I have significant limitations that affect activities of daily living*. Good*: I have moderate limitations that affect activities of daily living, no sports possible*. Very good*: I have only a few limitations with sports.* Excellent: *I am able to do whatever I wish (any sport) with no problems.*	Not improved at 1-5 yrs improved at 6-10 yrs N=3 Not improved at 1-5 yrs or at 6-10 yrs N= 15 No improvement from baseline was defined as a negative change or no change in overall condition score (OCS) from baseline to latest follow-up. Improvement was defined as a positive score changeof at least 1 point from baseline to latest follow-up
Pain (mean SD) 1 to 10 VAS	Preop 3.3 (3) N = 72 Yr 1-5 6.1 (3) N =72 Yr 6-10 5.3 (3) N=72 Improved patients only Yr 1-5 7.5 (2) N=50 Yr 6-10 7.4 (2.5) N=39
Swelling (mean SD) 1 to 10 VAS	Preop 4.3 (3) N = 72 Yr 1-5 6.8 (4.4) N =72 Yr 6-10 6.0 (4.5) N=72 Improved patients only Yr 1-5 7.5 (2) N=50 Yr 6-10 7.4 (2.5) N=39
Subgroup data given?	Satisfaction according to defect site subgroups.
Losses to follow-up - % and reasons if given. How analysed? Assumed to have failed	These covariate analyses were likely to be underpowered.
Any costs given?	No
Only for papers with survival curves	
Is curve Kaplan-Meier? If not, what is it?	Yes
Risk table attached?	No
Total events reported?	Yes
Hazard ratios, p value and/or 95% CI, and whether adjusted or not.	NA, no subgroups analysed so no HRs

*usually not given since repairs only in people with full thickness defect – i.e. cartilage defect down to bone.

** http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

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Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the study question or objective clearly stated?	Yes		
2. Was the study population clearly and fully described, including a case definition?	Yes		
3. Were the cases consecutive?		No	
4. Were the subjects comparable?			NA
5. Was the intervention clearly described?	Yes		
6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?			CD
7. Was the length of follow-up adequate?	Yes		
8. Were the statistical methods well-described?	Yes		
9. Were the results well-described?	Yes		
Quality Rating Fair to Good			
Additional Comments: *The large number of losses to follow up is worrying*			

*CD, cannot determine; NA, not applicable; NR, not reported

Nawaz 2014[23]	
Title	**Autologous Chondrocyte Implantation in the Knee Mid-Term to Long-Term Results**
Type of study	Case series
Quality of study	Good
Number of patients	869 met inclusion criteria. 41 lost to follow-up (1 died before study). 827 analysed
Population	N 827 Mean follow up (years) 6.2 [2-12] Mean age (years) 34 [14-56] Male (%) 59.6 Defect size (cm^2) 4.09 [0.64-20.7] Previous intervention 34% Defect site

	MF	51%
	LF	13%
	Pa	24.%
	Tr	6%
	Multi site	6%
Intervention	ACI-P/ACI-C /MACI	
Duration of injury?	NR	
Previous attempts at repair?	34% not including debridement and lavage – only previous microfracture, abrasion, drilling, ACI	
Size of defect in cm^2 Depth or severity if given*	Size see above. Patients with defect with estimated depth of >8 mm were not included. Lesions in the target population described as "regardless of depth or size".	
Duration of follow-up	See above	
Survival curve provided?	Yes	
Results		
Failure	Presented in KM plots. Data extracted elswhere.	
Stanmore functional rating (mean) P value from ANOVA adjusted for time of post op estimate	Preop Postop Mean difference 95% CI P	2.7 1.7 -1.09 -1.18 to -1.00 P<0.001
VAS (0-10) P value from ANOVA adjusted for time of post op estimate	Preop Postop Mean difference 95% CI P	5.95 3.561 -2.39 -2.61 to -2.19 P<0.001
Modified Cincinatti (0-100) P value from ANOVA adjusted for time of post op estimate	Preop Postop Mean difference 95% CI P	46.91 66.74 19.83 18.1 to 21.56 P<0.001
Complications	NR	
Subgroup data given?	Yes for KM plots of failure	
Losses to follow-up - % and reasons if given. How analysed? Assumed to have failed?	41 lost to follow up , 1 died ; 869-42 = 827 analysed.	
Any costs given?	No	
Only for papers with survival curves		
Is curve Kaplan-Meier? If not, what is it?	Yes. Several by subgroup	
Risk table attached?	To some	
Total events reported?	For some	
Hazard ratios, p value and/or 95% CI, and whether adjusted or not.	Yes for subgroup analyses; multivariate Cox regression.	

*usually not given since repairs only in people with full thickness defect – i.e. cartilage defect down to bone.

** http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

Quality Assessment Tool for Case Series Studies NIH

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the study question or objective clearly stated?	Yes		
2. Was the study population clearly and fully described, including a case definition?	Yes		
3. Were the cases consecutive?		No	
4. Were the subjects comparable?	Yes		
5. Was the intervention clearly described?	Yes		
6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes		
7. Was the length of follow-up adequate?	Yes		
8. Were the statistical methods well-described?	Yes		
9. Were the results well-described?	Yes		
Quality Rating Good			

*CD, cannot determine; NA, not applicable; NR, not reported

Niemeyer 2014[25]			
Title	**Long-term Outcomes After First-Generation Autologous Chondrocyte Implantation for Cartilage Defects of the Knee**		
Type of study	Case series		
Quality of study	Good		
Number of patients	70		
Population	N	70	
	16 were lost to follow-up		
	Mean follow up (years)	10.9	SD 1.1
	Mean age (years)	33.3	SD 10.2
	Male (%)	35.7	
	Defect size (cm^2)	6.5	SD 4.0
	Previous intervention (%)	62.8	
	Defect site		
	MF %	41.1	
	LF %	18.6	
	Pa %	20	

	Tr % 2.9 Multisite % 17.1
Intervention	First generation ACP
Duration of injury?	"the mean duration of symptoms was several years"
Previous attempts at repair? (	(44/70) 62.8% had previous intervention 20/44 were not defect associated
Size of defect in cm^2 Depth or severity if given*	Size see above. Full-thickness defects. Defects of the subchondral bone plate exceeding a depth of 3 to 4 mm were excluded.
Duration of follow-up	See above
Survival curve provided?	Yes
Results	
failure	KM plot
VAS pain (mean SD)	At follow-up, pain at exposure on the VAS decreased from 7.2 ± 1.9 pre-op to 2.1 ± 2.1 postop (P <.01)
Lysholm (mean SD)	42.0 ± 22.5 pre-op to 71.± 17.4 postop
IKDC (mean SD)	Follow up 74.0 ± 17.3
Tegner score (mean SD)	Decreased from 5.67 ± 2.39 to 4.36 ± 1.63 (P < 0.01). This represents slight worsening
 KOOS 4 KOOS pain KOOS symptoms KOOS ADL KOOS sports KOOS quality of life	Follow up scores Mean (SD) 68.4 ± 19.9 81.4 ± 18.2 75.6 ± 17.3 86.0 ± 16.7 62.3 ± 29.0 54.3 ± 23.9
Satisfaction (at follow up) Number	Very Satisfied 28 Satisfied 26 Neutral 14 Not Satisfied 2 Total 70
Complications	No complications related to the surgical procedure itself.
Subgroup data given?	Satisfaction according to defect site subgroups. Little difference but numbers too small for conclusions
Losses to follow-up - % and reasons if given. How analysed? Assumed to have failed? (Don't expect details to be provided – case series will probably only include those not lost to F-U)	16 were lost to follow-up; no details
Any costs given?	No
Only for papers with survival curves	
Is curve Kaplan-Meier? If not, what is it?	Yes
Risk table attached?	No
Total events reported?	Yes
Hazard ratios, p value and/or 95% CI, and whether adjusted or not.	NA, no subgroups analysed

*usually not given since repairs only in people with full thickness defect – i.e. cartilage defect down to bone.

Quality Assessment Tool for Case Series Studies NIH

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the study question or objective clearly stated?	Yes		
2. Was the study population clearly and fully described, including a case definition?	Yes		
3. Were the cases consecutive?		No	
4. Were the subjects comparable?	Yes		
5. Was the intervention clearly described?	Yes		
6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes		
7. Was the length of follow-up adequate?	Yes		
8. Were the statistical methods well-described?	Yes		
9. Were the results well-described?	Yes		
Quality Rating Good			
Additional Comments: *The large number of losses to follow up is worrying*			

*CD, cannot determine; NA, not applicable; NR, not reported

Niemeyer 2014[4]	**Data**
Title	First-generation versus second-generation autologous chondrocyte implantation for treatment of cartilage defects of the knee: a matched-pair analysis on long-term clinical outcome
Type of study	Cohort with matched historical controls Criteria for matching were defect location, and patient age. If there were multiple options in the database, defect size was used an additional parameter for selection
Quality of study	Good. 5 stars .Newcastle/Ottawa
Number of patients	N=46 ACI-P = 23 ACI-P were the historical controls ACI-C = 23
Population	Age mean (SD): ACI-P 31.7 (6.9), ACI-C 31.4 (7.8)

	% male not reported Reason for injury not reported
Intervention	ACI-P (Chondrocytes provided by Genzyme, Cambridge, USA and Metreon Bioproducts GmbH, Freiburg, Germany) ACI-C (Chondrogide™, Geistlich, Wolhusen, Switzerland)
Duration of injury?	Not reported
Previous attempts at repair?	Not reported
Size of defect in cm^2 mean, (SD) Depth or severity if given*	ACI-P: 5.1 (2.3) ACI-C: 4.9 (1.5) All graded III or IV according to the ICRS classification
Duration of follow-up, mean (SD)	ACI-P: 10.7 (1.0) years ACI-C: 10.5 (0.6) years
Survival curve provided?	Yes
Results	
Re-intervention rate Definition for re-intervention not given	ACI-P: 4/23 (17.4%), including one total knee joint replacement ACI-C: 4/23 (17.4%) including one total knee joint replacement
Lysholm score, mean SD	ACI-P: Preop 38.4 (18.3) Follow-up 75.6 (11.8) ACI-C: Pre-op 44.1 (21.3) Follow-op 82.7 (9.9) ACI-P vs ACI-C preop: p=0.371 ACI-P vs ACI-C at follow-up: p=0.031
No baseline data	ACI-P: 68.0 (12.0) ACI-C: 76.4 (12.8) P=0.023
Subgroup data given?	No subgroup data
Losses to follow-up - % and reasons if given. How analysed? Assumed to have failed? ()	Not applicable
Any costs given?	No
Only for papers with survival curves	
Is curve Kaplan-Meier? If not, what is it?	- yes -
Risk table attached?	no

Total events reported?	no
Hazard ratios, p value and/or 95% CI, and whether adjusted or not.	No

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE-COHORT STUDIES [71]

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort

a) truly representative of the average _____ (describe) in the community □

b) somewhat representative of the average _____ in the community □ □**yes (proportion of men not reported. Patients with a minimum of 10 years follow-up selected)**

c) selected group of users eg nurses, volunteers

d) no description of the derivation of the cohort

2) Selection of the non exposed cohort

a) drawn from the same community as the exposed cohort □

b) drawn from a different source **yes**

c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure

a) secure record (eg surgical records) □ □**yes**

b) structured interview □

c) written self report

d) no description

4) Demonstration that outcome of interest was not present at start of study **Not applicable**

a) yes □

b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis

a) study controls for **defect location and patient age** (select the most important factor) □ □ **yes**

b) study controls for any additional factor □ (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome

a) independent blind assessment □

b) record linkage □

c) self report

d) no description **yes**

2) Was follow-up long enough for outcomes to occur

a) yes (select an adequate follow up period for outcome of interest) □ □**yes**

b) no

3) Adequacy of follow up of cohorts

a) complete follow up - all subjects accounted for □ **yes**

b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) □

c) follow up rate < ____% (select an adequate %) and no description of those lost

d) no statement

Peterson 2010[26]	**Data**
Title	Autologous Chondrocyte Implantation: A Long-term Follow-up
Type of study	Case series Retrospective data collection and analysis
Quality of study	Poor
Number of patients	590 had ACI-P 341 eligible 224 responded to questionnaires Isolated cartilage lesions n=159 Multiple lesions n=56
Population	Age 33.3 years (SD 9.5, range 14-61.5) % male not reported Reason for injury not reported
Intervention	ACI-P
Duration of injury?	Not reported
Previous attempts at repair? (Don't count debridement and lavage – only previous microfracture, abrasion, drilling, ACI)	30/82 (37%) had a previous operation that included drilling or shaving of the chondral lesion. Not clear what the n of 82 relates to.
Size of defect in cm^2 Depth or severity if given*	5.3 cm^2 (range, 0.6-15.8) per lesion 7 cm^2 (range 0.6-27) per patient
Duration of follow-up	12.8 years (range 9.3-20.7)
Survival curve provided?	No
Results	
	At follow-up Better or same: 165/224 (74%)

	Worse: 59/224 (26%) Satisfied with ACI and would do again: 202/219 (92%) Success/failure not reported. Current status during the past 10 years rated as better, worse, or unchanged (no further details).
Lysholm score	Preop: 60.3 Follow-up: 69.5 (P = 0.009 from 2-sample t test, p= 0.0016 from paired t test pertaining to 58 patients)
Tegner-Walgren score	Preop: 7.22 Follow-up: 8.2 (p= 0.002 from 2-sample t test, p=0.0008 from paired t test pertaining to 109 patients)
Brittberg-Peterson score. 10cm VAS with 13 parameters, where 0 relates to normal function and 130 severe disability	Preop: 59.4 Follow-up: 40.9 (p< 0.001 from 2-sample t test, P =0 .004 from paired t test pertaining to 53 patients).
KOOS scores	No baseline data. Follow-up: Pain 74.76 Symptoms 63 Activities of daily living 81 Sports 41.5 QOL 49.3
Noyes score	Follow-up: 5.4
Subgroup data	
Improved compared with previous years, n (%)	Isolated femoral condyle defects (n=52): 14 (27) Multiple lesions (n=55): 12 (22) Osteochondritis dissecans lesions (n=26): 7 (27) Patellar lesions with realignment (n=34): 6 (18) Femoral condyle lesions with anterior cruciate ligament reconstruction (n=46): 11 (24)
Same compared with previous years, n (%)	Isolated femoral condyle defects (n=52): 22 (42) Multiple lesions (n=55): 20 (40) Osteochondritis dissecans lesions (n=26): 14 (54) Patellar lesions with realignment (n=34): 18 (53) Femoral condyle lesions with anterior cruciate ligament reconstruction (n=46): 24 (52)
Would do ACI again, n (%)	Isolated femoral condyle defects (n=52): 47 (90) Multiple lesions (n=55): 51 (94)

	Osteochondritis dissecans lesions (n=26): 25 (96.2) Patellar lesions with realignment (n=34): 31 (91.2) Femoral condyle lesions with anterior cruciate ligament reconstruction (n=46): 41 (91.1)
Lysholm score, mean (range) [available number of values]	Isolated femoral condyle defects (n=52) Preop: 60.1 (46-81) [13] Follow-up: 72.6 (25-96) p=0.02 (2-sample t test) p=0.03 (paired t test) Multiple lesions (n=55) Preop: 50.9 [8] Follow-up: 67.7 (17-100) p=0.05 (2-sample t test) p=0.15 (paired t test) Osteochondritis dissecans lesions (n=26) Preop: 56.2 (SD 22, range 13-85) [12] Follow-up: 67.4 (SD 16.4), (31-95) p=0.1 (2-sample t test) p=0.3 (paired t test) Patellar lesions with realignment (n=34) Preop: 69 (47-85) [6] Follow-up: 66 (17-100) p=0.8 (2-sample t test) p=0.3 (paired t test) Femoral condyle lesions with anterior cruciate ligament reconstruction (n=46) Preop: 59.1 [16] Follow-up: 69.2 (34-100) p=0.05 (2-sample t test) p=0.1 (paired t test)
Tegner-Wallgren score, mean (range) [available number of values]	Isolated femoral condyle defects (n=52) Preop: 7.8 [26] Follow-up: 8 (2-14) p=0.7 (2-sample t test) p=0.7 (paired t test) Multiple lesions (n=55) Preop: 7.2 [22] Follow-up: 8 (3-11) p=0.1 (2-sample t test) p=0.2 (paired t test) Osteochondritis dissecans lesions (n=26) Preop: 6.4 (SD 2.2, range 1-9) [16] Follow-up: 8.6 (SD 1.6, range 5-13) p=0.01 (2-sample t test) p=0.03 (paired t test)

	Patellar lesions with realignment (n=34) Preop: 7.4 (3-14) [17] Follow-up: 8.1 (3-14) p=0.3 (2-sample t test) p=0.2 (paired t test) Femoral condyle lesions with anterior cruciate ligament reconstruction (n=46) Preop: 7.2 [33] Follow-up: 8.1 (3-15) p=0.1 (2-sample t test) p=0.07 (paired t test)
Brittberg-Peterson score, mean (range) [available number of values]	Isolated femoral condyle defects (n=52) Preop: 65.9 (31-107) [12] Follow-up: 38.4 (3-102.8) p=0.02 (2-sample t test) p=0.08 (paired t test) Multiple lesions (n=55) Preop: 64.1 [8] Follow-up: 46.3 (1.7-115.8) p=0.12 (2-sample t test) p=0.9 (paired t test) Osteochondritis dissecans lesions (n=26) Preop: 51.8 (SD 32, range 9.4-104) [11] Follow-up: 38.6 (SD 29, range 2.7-99) p=0.3 (2-sample t test) p=0.8 (paired t test) Patellar lesions with realignment (n=34) Preop: 50.1 (31-65) [6] Follow-up: 49.2 (31-65) p=0.9 (2-sample t test) p=0.5 (paired t test) Femoral condyle lesions with anterior cruciate ligament reconstruction (n=46) Preop: 56.3 [14] Follow-up: 41.1 (2-103.4) p=0.08 (2-sample t test) p=0.2 (paired t test)
KOOS score	Isolated femoral condyle defects (n=52): Pain 77.3 Symptoms 65 ADL 83.1 Sports 45.1 QOL 51 Multiple lesions (n=55): Pain 71.3 Symptoms 61.5 ADL 77.8

	Sports 37.4 QOL 51 Osteochondritis dissecans lesions (n=26): Pain 78 Symptoms 65.2 ADL 85.6 Sports 46.9 QOL 54.3 Patellar lesions with realignment (n=34): Pain 69.7 Symptoms 57.9 ADL 75 Sports 34.4 QOL 44.1 Femoral condyle lesions with anterior cruciate ligament reconstruction (n=46): Pain 72.8 Symptoms 67.5 ADL 81.3 Sports 41.1 QOL 48.2
Noyes score, mean range	Isolated femoral condyle defects (n=52): 5.4 (1-9). States 5.4 in text, 5.3 in table. Multiple lesions (n=55): 5.2 (1-10) Osteochondritis dissecans lesions (n=26): 5.7 (3-9) Patellar lesions with realignment (n=34): 5.1 (1-10) Femoral condyle lesions with anterior cruciate ligament reconstruction (n=46): 5.2 (1-9)
Losses to follow-up - % and reasons if given. How analysed? Assumed to have failed?	224/341 (65%) responded to questionnaires. Only responders included in analysis.
Any costs given?	No
Survival curve	No

Quality Assessment Tool for Case Series Studies

Criteria	**Yes**	**No**	**Other (CD, NR, NA)***

1. Was the study question or objective clearly stated?	y		
2. Was the study population clearly and fully described, including a case definition?		n	
3. Were the cases consecutive?			CD
4. Were the subjects comparable?	y		
5. Was the intervention clearly described?	y		
6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?		n	
7. Was the length of follow-up adequate?	y		
8. Were the statistical methods well-described?	y		
9. Were the results well-described?		n	
Quality Rating Poor			
Additional Comments: Pre-operative values not available for some outcomes. Baseline measures collected retrospectively from medical files.			

*CD, cannot determine; NA, not applicable; NR, not reported

Salzman 2013[29]	**Data**
Title	Reoperative characteristics after microfracture of knee cartilage lesions in 454 patients
Type of study	Case series
Quality of study	Fair
Number of patients	560 consecutive patients of which 454 were evaluated and 123 found to have been re-operated on the index lesion. Mean Follow up for the 123 receiving reoperation was 5 years (SD 2.1)
Population	N 123 Age at surgery, 44.2 ± 13.9 years Male/female: 67/56 BMI, kg/m^2 25.8 ± 3.6 Smoking/non-smoking: 30/93
Intervention	Microfracture
Duration of injury?	Symptom duration: 61.3 ± 68.6 months
Previous attempts at repair? (Don't count debridement and lavage – only previous microfracture, abrasion, drilling, ACI)	Number of Previous surgeries : 1.9 ± 2.1

Size of defect in cm^2 Depth or severity if given* All 123 had one defect or more; 22 had 2 defects; 2 had 3 defects. So 99 had only one defect 22 had two defects 2 had three defects Commonest depth for defect: ICRS °3C and ICRS °3B. Very few ICRS °2 or ICRS °4 ICRS = International Cartilage Repair Society	# of defects 1.2 ± 0.5 Defect size/knee, cm^2 2.1 ± 1.7 Defect # 1 (n = 123) #2 (n = 22) #3 (n = 2) 99 with 1 defect, depth according to ICRS ICRS °2 # 1 ICRS °3B # 26 ICRS °3C # 36 ICRS °4 # 36 22 with second defect (depth of largest) ICRS °2 # 1 ICRS °3B # 5 ICRS °3C # 12 ICRS °4 # 4 2 with third defect (depth of largest) ICRS °2 # 0 ICRS °3B # 0 ICRS °3C # 1 ICRS °4 # 1
Duration of follow-up	Mean Follow up for the 123 receiving reoperation was 5 years (SD 2.1) On average reoperation commenced 18 months after initial microfracture
Survival curve provided?	No
Results	
Definitions of success and failure	Failure defined as above
Lysholm score mean (SD)	Preop not reported Postop Lysholm: 62.8 ± 24.5
VAS knee pain, mean (SD) Numeric analogue scale (NAS) for pain (NAS-P) with 10 representing ‘‘no pain’’ and 0 representing ‘‘maximal imaginable pain.’’	Preop NAS-P 3.1 ± 2.1 N 123 Postop NAS-P 5.2 ± 2.4 N123
VAS knee function, mean (SD)	NAS F definition unclear. Preop NAS-F 2.8 ± 1.8 Postop NAS-F 4.8 ± 2.2
Subgroup data	
Failure	Findings based on regression analysis. Failure was associated with the following factors: Smaller lesions; more previous surgery; preop subjective sensation of less pain and less function; smoking; patella-femoral defects.
VAS knee pain, mean (SD)	NR
VAS knee function, mean (SD)	NR
Losses to follow-up - % and reasons if given. How analysed? Assumed to have failed?	Telephone interviews of some of the 560 patients were incomplete leaving 454 for analysis
Any costs given?	No
Survival curve?	No

Quality Assessment Tool for Case Series Studies NIH

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the study question or objective clearly stated?	y		
2. Was the study population clearly and fully described, including a case definition?	y		
3. Were the cases consecutive?			CD
4. Were the subjects comparable			NA
5. Was the intervention clearly described?	y		
6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?		N	
7. Was the length of follow-up adequate?	y		
8. Were the statistical methods well-described?	y		
9. Were the results well-described?	y		
Quality Rating Fair			

*CD, cannot determine; NA, not applicable; NR, not reported

Shive 2015[30]			
Title	**BST-CarGel® Treatment Maintains Cartilage Repair Superiority over Microfracture at 5 Years in a Multicenter Randomized Controlled Trial**		
Type of study	RCT		
Quality of study	Fair		
Number of patients	80 Originally randomised; THIS report n=60		
Population The trial randomised 41 & 39 to BST and MF respectively; this data is only for those followed to 5 (?) years Inclusion if single, focal cartilage lesion on the femoral condyles and moderate knee pain (>4 on a 10 cm VAS).		BST-CarGel	MF
	N	34	26
	Mean follow up	NR	NR
	Age mean (SD) yrs	34.3 (9.7)	40.1 (10.1)
	Male (%)	64.7	53.8
	Defect size (cm^2)		
	mean (SD)	2.41 (1.5)	2.08 (1.22)
	max	6.77	4.46
	BMI (kg/m^2) mean (SD)	27.6 (2.7)	25.7 (2.9)
	Symptom duration yrs		
	Median[range]	1.4 [0.1-19.6]	3 [0.3-27.8]
	Activity level N (%)		
	High	16 (47.1)	15 (57.5)

	Medium 16 (47.1) 11 (42.3) Low 2 (5.8) 0 (0) Previous intervention NR NR
Intervention	MF or enhanced MF with BST-CarGel® multiple surgeons
Duration of injury?	See above
Previous attempts at repair?	NR
Size of defect in cm^2 Depth or severity if given*	See above. Full thickness.
Duration of follow-up	Appears to be 5 years
Survival curve provided?	No
Results	
Failure	NR
Lesion % fill. least squares means ± standard error	BST-CarGel MF N 34 26 % fill 93.79% ± 1.16% 86.96% ±2.85% P=0.017
WOMAC Change from baseline. (least squares means ± standard error adjusted for baseline)	BST-CarGel MF Pain N 33 26 score -15.37 ± 1.47 -16.56 ± 1.19 Stiffness N 33 26 score −5.63 ± 0.72 −6.68 ± 0.58 Physical Function N 33 26 score −56.52 ± 4.57 −62.10 ± 3.43 no significant differences between groups
SF 36 Change from baseline (least squares means ± standard error adjusted for baseline)	**Physical component** BST-CarGel MF N 34 27 score 13.12 ± 1.63 14.48 ± 1.42 **Mental component** BST-CarGel MF N 34 27 Score 2.72 ± 1.30 −0.17 ± 1.76 No significant differences between groups.
Mean T2 MRI relaxation time (ms). (least squares means ± standard error)	BST-CarGel MF N 29 22 75.68 ± 5.25 90.41 ± 6.56 Aberrant data points for some patients were discarded. P=0.026
Complications	NR
Subgroup data given?	No
Losses to follow-up - % and reasons if given. How analysed? Assumed to have failed?	25% of patients lost to follow up.
Any costs given?	No
Survival curve?	No

*usually not given since repairs only in people with full thickness defect – i.e. cartilage defect down to bone.

Shive 2015 **Quality Assessment Tool for RCT**

Bias	**Author judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Via telephone interactive voice response system with use of a central,computer generated randomization schedule.
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias)	Low risk	MRI assessments were blinded
Blinding of outcome assessment (detection bias)	Unclear risk	Patients not blinded because of incision size, bias in responses to questionaires possible
Incomplete outcome data (attrition bias)	High risk	25% of patients missing at 5 year follow up
Selective reporting (reporting bias)	Unclear risk	Some non primary outcomes appear to have been selected.
Other bias	Low risk	None identified

Solheim 2014[32]	**Data**
Title	Results at 19-14 years after microfracture treatment of articular cartilage defects in the knee. Follow up to 2010 paper.
Type of study	Case series
Quality of study	Fair 12 years median follow up (range 10-14) was reported for 110 (?) patients. Because baseline values differ between 2010 and 2014 papers it is possible fewer than 110 were analysed in 2014
Number of patients	2010 paper 116 eligible, 110 included in analysis; median age 38 years (range 15–60). *2014 paper* *Included patients aged 60 years or younger.* Patients having had a knee replacement (in the ipsilateral knee during the observation period) were denoted as failure, and their outcome score was not included in the calculations(of Lysholm score and VAS outcomes).
Population	Age 38 years (range 15–60) 58% male Reason for injury not reported Based on 110 analysed
Intervention	Microfracture
Duration of injury?	Median 40 months (range 1 month–20 years)
Previous attempts at repair?	Not reported
Size of defect in cm^2 Depth or severity if	One (n = 76), two (n = 27) or three (n = 7) lesions with a median total treated area of 4 cm^2 (range 1–15)

given*	Subgroups: Single cartilage defect: mean 3.8 cm^2 (SD 1.5) Multiple defects mean 7.5 cm^2 (SD 3.0)
Duration of follow-up	Median 5 years (range 2–9) *Median 12 (range 10 14) in 2014 paper.*
Survival curve provided?	No (lacking both publications)
Results	
Definitions of success and failure Failure defined as a new surgical procedure with the intention to treat the cartilage lesion Lysholm score (e.g. another cartilage repair procedure, an osteotomy or a knee replacement). .	Failures: 24/110 (22%) Improved Lysholm score in non-failures: 67/86 (78%). Definition of 'improved' not reported. *The 2014 paper: Patients having had a knee replacement (in the ipsilateral knee during the observation period) were denoted as failure, and their outcome score was not included in the calculations (of Lysholm score and VAS outcomes).* *The percentage patients with Failure/poor result was 47% (at medium term) and 45.5% (at 10-14 years). Failure (n=7) was defined as above, and "poor result" was defined as a Lysholm score of 64 or less or having a knee replacement.*
Lysholm score mean (SD)	Pre-op: 51 (18) Follow-up: 71 (23) p<0.001 *<u>In 2014 paper:</u>* *Pre-op: 49(18)* *"Medium follow up" in 2014 67 (23)* *Follow up (10-14 yrs) 65 (24) The number of failures =7 (omitted from calculation)* *"Medium follow up" in 2014 67 (23) [not 71 (23) as in 2010].* *Presumably : 65 -7 = 58 "poor" but without knee replacement at 10-14 years follow up.*
VAS knee pain, mean (SD) Grading of knee pain and function of the knee by patient-administered visual analog scales (VAS): 0 = no pain to 100 = worst possible pain .	Pre-op: 52 (22) Follow-up: 30 (24) p<0.001 *<u>In 2014 paper:</u>* *Pre-op: 55(21)* *Medium follow up 34 (24)* *Follow up (10-14 yrs) 31 (24) The number of failures =7 (omitted from calculation)* *2014 medium follow up 34 (24) not same as 2010 [30 (24)]*
VAS knee function, mean (SD) VAS function: 0 = useless to 100 = full function	Pre-op: 41 (23) Follow-up: 69 (22) p<0.001 *<u>In 2014 paper:</u>* *Pre-op: 40 (22)* *Medium follow up 63 (23)* *Follow up (10-14 yrs) 65 (28) The number of failures =7 (omitted from calculation)*
Subgroup data	Failures: Single chondral lesion 14/76 (18%) Multiple lesions 10/34 (29%) Improved Lysholm score in non-failures: Single chondral lesion 50/62 (18%)

	Multiple lesions 17/24 (29%)
Lysholm score mean (SD)	Single defect Pre-op: 53 (17) Follow-up: 74 (21) p<0.001 Multiple defects Pre-op: 46 (21) Follow-up: 63 (24) p=0.005 *<u>In 2014 paper:</u>* *A subgroup (n=30) with ≤40 preop score had a poorer 10-14 yrs score than >40 preop group: 56 (24) versus 68 (22) P 0.02* *No relationship found between preop age or size of defect and 10-14 yrs follow up score.* *Poor outcome (score of ≤ 64) at 10-14 yrs (in 50 of 110 , 45.5%) was associated with following subgroups: A] signs of degenerative change around lesion at time of surgery (signs 54% poor versus no signs 34% poor, P 0.04; b] previous or concurrent partial medial meniscectomy in ipsilateral knee (59% poor versus 40% poor, P 0.048 ; c] A ≤40 preop Lyshol m score (60% poor versus 39%, P 0.047; d] ≥36 months preop duration of symptoms (52% poor versus 30% , P 0.047)* *Percentages only reported (no n/N data)* *If 110 were analysed the* *N in each subgroup would appear to be:* *a]Signs = 63 | no signs = 47;* *b]Minisc = 32 | No minisc = 78* *c]≤40 = 34 * | > 40 =76* *d]≥36 mos = 32 | <36 = 78* ** this number should be 30, the discrepancy may be due to rounding of percentages and that fewer than 110 were in fact analysed.*
VAS knee pain, mean (SD)	Single defect Pre-op: 52 (22) Follow-up: 26 (21) p<0.001 Multiple defects Pre-op: 53 (22) Follow-up: 41 (27) p=0.018
VAS knee function, mean (SD)	Single defect Pre-op: 41 (24) Follow-up: 74 (19) p<0.001 Multiple defects Pre-op: 40 (19) Follow-up: 54 (24) p=0.009
Losses to follow-up - % and reasons if given. How analysed? Assumed to have failed?	6/116 (5.2%) excluded from analysis (2 died, 4 lost to follow-up or refused).
Any costs given?	No
Survival curve?	No

Quality Assessment Tool for Case Series Studies NIH

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the study question or objective clearly stated?	y		
2. Was the study population clearly and fully described, including a case definition?	y		
3. Were the cases consecutive?			CD
4. Were the subjects comparable	y		
5. Was the intervention clearly described?	y		
6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?		N	
7. Was the length of follow-up adequate?	y		
8. Were the statistical methods well-described?	y		
9. Were the results well-described?	y		
Quality Rating Fair			
Additional Comments: 'Improvement' on Lysholm scale not defined			

*CD, cannot determine; NA, not applicable; NR, not reported

Steadman 2003[34]	
Title	**Outcomes of Microfracture for Traumatic Chondral Defects of the Knee: Average 11-Year Follow-up**
Type of study	Case series
Quality of study	Fair
Number of patients	72 (75 knees) met inclusion criteria; 68 (71 knees) included in results analysis.
Population	mean age (range): 30.4 years (13-35 years) 66.2% male Reason for injury? Either traumatic or degenerative. Acute: 15 knees ;Chronic: 56 knees.
Intervention	Microfracture
Duration of injury?	Mean 3.2 [0.02-16.1] years
Previous attempts at repair?)	Unclear
Size of defect in cm^2	2.77cm^2 (range, 0.2-10 cm^2). Full thickness.

Depth or severity if given*	
Duration of follow-up	Mean 11.3 years (range 7-17 years)
Survival curve provided?	NO
Results	
MF failure	2. Extremely low rate; definition of failure not clear
Questionnaire scales vary: final v pre-op. Satisfaction 1-10 Pain 1-4 Swelling 1-4 ADL 1-10 Strenuous work 1-10 Sport 1-10	All scores represent clinical improvement mean SD range 8.3 1.6 4-10 -1.5 0.9 -3-1 -1.5 1 -3-1 2.8 2.6 -3-8 2.7 3 -4-9 2.9 3.4 -4-8
Tegner final v pre-op 1-10 best	mean SD range 2.7 1.7 -1-6 Assume this is mean of the individual score changes
Lysholm final v pre-op 1-100 best	mean SD range 30.1 12.3 4-61 Assume this is mean of the individual score changes
Satisfaction	See above
Complications	"No perioperative complications were related to the surgical procedure". Others not reported.
Subgroup data given?	
Lysholm Age Chronicity Location Size of lesions	Multivariate linear regression. Coefficient P -0.299 0.011 -0.084 0.466 -0.226 0.066 -0.146 0.225 Age is only influential factor and has negative effect on Lysholm score
Losses to follow-up - % and reasons if given. How analysed? Assumed to have failed?	2 reasons given; also 2 patients considered failures were not included in analyses.
Any costs given?	No
Survival curve?	No

Quality Assessment Tool for Case Series Studies NIH

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the study question or objective clearly stated?	Yes		

2. Was the study population clearly and fully described, including a case definition?	Yes		
3. Were the cases consecutive?		NO	
4. Were the subjects comparable?	Yes		
5. Was the intervention clearly described?	Yes		
6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes		
7. Was the length of follow-up adequate?	Yes		
8. Were the statistical methods well-described?	Yes		
9. Were the results well-described?	Yes		
Quality Rating Fair			
Additional Comments (If POOR, please state why): *The selection of participants was clearly retrospective and not consecutive (i.e. 25% of 302 consecutive patients were included). There was no mention of any re-intervention after MF. Only two MFs were judged failures, but no clear criteria for failure was offered. Outcome measures were subjective and some designed for this study only (not validated). Some patients with poor outcome were omitted from analyses.*			

*CD, cannot determine; NA, not applicable; NR, not reported

Vanlauwe 2011[1]	**Data**	
Title	**Five-Year Outcome of Characterized Chondrocyte Implantation Versus Microfracture for Symptomatic Cartilage Defects of the Knee**	
Type of study	RCT	
Quality of study	Uncertain risk of bias [Based on risk of selection bias (Cochrane risk of bias tool); see below]	
Number of patients	Total 112: ACI 57 (51 treated); Microfracture 61	
Population Duration of injury? Previous attempts at repair?	NOTE 6 CCI did not get treated	
	CCI	MFR
	N 57	61
	Age, years 33.9 ± 8.5	33.9 ± 8.6
	Height, cm 176.5 ± 10.8	177.0 ± 8.5
	Weight, kg 78.3 ± 13.9	80.6 ± 13.3
	Male N (%)	41 (67)

	35 (61) Female N (%) 20 (33) 22 (39) Duration since onset, years (median, range) 1.57 (0-18) 1.97 (0-18) Proportion with previous surgery* any 77% 88% Number (%) with previous surgeries = 0 14 (23) 7 (12) Number (%) with previous surgeries = 1 34 (56) 29 (51) Number (%) with previous surgeries ≥2 13 (21) 21 (37) Defect size, cm2 2.4 ± 1.2 2.6 ± 1.0
Intervention	ACI-P: ChondroCelect Microfracture: as Steadman
Size of defect Depth or severity if given*	See above, ICRS grade III or IV. Deep lesions.
Duration of follow-up	5 years
Survival curve provided?	Yes
Results	
Failures	ACI: 7/51 (13.7%) Microfracture 10/61 (16.4%) log rank P = 0.561 Failure defined as re-intervention
KOOS	Change from baseline at 5 years ACI MF DIFF (95% CI) P Overall KOOS 21.17 ± 2.88 14.07 ± 2.54 7.1 (-0.52, 14.73) 0.068 Activities of daily living 16.42 ± 2.97 11.35 ± 2.62 5.07 (-2.79, 12.94) 0.203 Pain 19.04 ± 3.17 13.27 ± 2.74 5.77 (-2.55, 14.09) 0.172 Symptoms/stiffness 17.70 ± 2.82 10.90 ± 2.52 6.81 (-0.70, 14.32) 0.075 Quality of life 32.12 ± 4.30 21.23 ± 3.87 10.89(-0.59, 22.38) 0.062 Function, sports & recreational 32.50 ± 5.88 22.98 ± 5.69 9.52 (-6.87, 25.90) 0.25
KOOS subgroup	Change from baseline at 5 years, patients with < 3 years of symptoms. Pre-planned subgroup ACI MF Overall KOOS 25.96 ± 3.45 15.28 ± 3. Activities of daily living 18.95 ± 3.46 12.53 ± 3. Pain 22.86 ± 3.66 13.75 ± 3. Symptoms/stiffness 21.43 ± 3.47 13.34 ± 3. Quality of life 40.51 ± 5.47 21.48 ± 5. Function, sports and recreational activities 40.15 ± 7.66 24.85 ± 7.
Adverse events	Over 5 years 42 (82%) and 38 (62%) ACI and MF patients experienced at least one treatment emergent adverse events

Mean Tegner score	NR
Subgroup data	See above for oKOOS
Number of failures by 5 years	See above
Losses to follow-up -	Six of 57 in the ACI arm did not receive treatment
Any costs given?	No
Only for papers with survival curves	
Is curve Kaplan-Meier? If not, what is it?	Yes
Risk table attached?	Yes (but for the MF arm does not appear sensible)
Total events reported?	Yes
Hazard ratios, p value and/or 95% CI, &whether adjusted	No. Log rank test p value. No adjustment.

*usually not given since repairs only in people with full thickness defect – i.e. cartilage defect down to bone.

Bias	**Author judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Minimization not fully described
Allocation concealment (selection bias)	Low risk	Allocation through an IVRS system
Blinding of participants and personnel (performance bias)	High risk	Patients not blinded bias likely but unclear
Blinding of outcome assessment (detection bias)	Unclear risk	MRI independent center carrying out the analyses of primary end points was unaware of patient treatment
Incomplete outcome data (attrition bias)	Low risk	Follow up complete for treated patients
Selective reporting (reporting bias)	Low risk	KOOS and adverse events pre specified and reported
Other bias	Unclear risk	Errors in risk table for KM plot

Appendix 3 Excluded Studies

Author ID/Year	Reason
Adachi 2014[72]	The procedure described seems to be about implantation of cartilage-like tissue rather than chondrocytes.
Bert 2015[37]	Editorial and opinion piece with no primary data
Bae 2013[42]	All had Kellgren-Lawrence score of 3. EMA MAC SPC excluded such patients Patients had OA and mean age 62.1 years so would not be considered for ACI.
Behery 2014[73]	Systematic review. Used only for checking completeness of our search retrieval. Six studies with 50 patients in case series;
Brix 2012[74]	The 8 years details are too sparse to be of much use. It's only an abstract and we have other much better ACI data.
Briggs 2013 (abstract)[75]	Mean follow-up only 4 years. No data on subgroup with longer FU
Ebert 2013[76]	Has patients from reference Ebert 2011[7]
Ebert 2011[7]	Case series Matrix-induced autologous chondrocyte implantation (MACI) Excluded because almost half had concomitant procedures. No FU beyond 5 years.
Ebert 2013_ENREF_4[77]	Includes too many patients having concomitant procedures.
Filardo 2012[78]	Second-generation autologous chondrocyte implantation Hyalograft C
Filardo 2013[79]	Hyaluronan-based scaffold Hyaff 11 (Fidia Advanced Biopolymers Laboratories, Padua, Italy).
Filardo 2014 [80]	The first procedure was a biopsy of healthy cartilage for autologous chondrocyte culture and subsequent seeding onto the scaffold (made of a benzylic ester of hyaluronic acid consisting of a network of 20-**m**m-thick fibers with interstices of variable sizes: HYAFF 11, Fidia Advanced Biopolymers Laboratories, Padova, Italy). The second step was the arthroscopic implant of the bioengineered tissue Hyalograft C (Fidia Advanced Biopolymers Laboratories) through
Gobbi 2014[8]	Excluded because large proportion had concomitant surgery such as meniscectomy, ACRL,
Filardo 2014[81]	Hyalograft C (Fidia Advanced Biopolymers Laboratories)
Gooding 2006[3]	Only 2 years follow-up
Gudas 2012[36]	Mosaic-type osteochondral autologous transplantation (OAT) and microfracture but only 30 patients in each arm
Health Quality Ontario[82]	Not about MF or ACI
Kon 2009 [83]	Second-generation autologous chondrocyte implantation Hyalograft

	C
Kon 2011[84] Abstract	Biocompatible and biodegradable hyaluronian based scaffold (hylograft C)
Kon 2011[47]	Arthroscopic Hyalograft C technique
Kon 2011[85]	Second-generation autologous chondrocyte implantation (Hyalograft C)
Kon 2009[86]	Systematic review
Kreuz 2006[87]	Follow-up too short
McNickle 2009[88]	Follow-up too short
Minas 2012[89]	Follow-up only 12 months
Minas 2014[44]	
Mithoefer 2009 [90]	SR. Mentions only 5 studies with FU > 5 years. Check Gill Am J Knee Surg 2000/13/33-40
Mithoefer 2012[91]	Review. Mentions only 5 studies with FU > 5 years.
Nawaz 2011 (Abstract)[92]	Only an abstract
Ebert 2011 (abstract)[93]	Case series abstract only N= 41 patients (44 knees; 53 grafts)
Negrin 2013[94]	 Follow-up 2-5 years
Negrin 2012[95]	Most studies in meta-analysis had follow-up only 2 years. Some had 5 years but we have the individual trials
Neimeyer 2010[96]	Follow-up too short.
Noyes 2013[97]	Review. Checked for studies.
Oussedik 2015[98]	SR. We have all the individual trials that are eligible
Peterson 1998[99]	Unavailable
Rosenberger 2008[100]	Mean follow-up < 5 years and quite a lot had other procedures such as osteotomy so pure ACI <40 patients
[35]	Minimum postoperative follow-up of 2 years Follow up time, year: 4.2 ± 1.8
Sciarretta 2013[101]	19 patients PVA-H hydrogel implants
Scillia 2015[102]	Not ACI or MF. debridement
Ulstein 2014[103]	microfracture technique (MF) versus osteochondral autologous transplantation (OAT Mosaicplasty) MF N=11 OAT Mosaicplasty N=14

Upmeier 2007[104]	Follow up costs Patients had to have been diagnosed with knee cartilage defects and, according to their operation record, treated between 1997 and 2001 with any of the following techniques : autologous chondrocyte implantation, osteochondral allografts or autografts, microfracture or subchondral drilling, chondroplasty/laser chondroplasty, abrasion arthroplasty, debridement/cartilage shaving (without further information)
Wylie 2015[105]	Systematic review
Zak 2012[106]	2-step procedure, a biopsy sample was arthroscopically harvested to culture the cells and to seed them on a matrix (MACI [Genzyme, Cambridge, Massachusetts], 15 patients;HyalograftC [Fidia Advanced Biomaterials, Abano Terme, taly], 44 patients; CaReS [Arthro Kinetics Biotechnology GmbH, Krems, Austria], 11 patients).

Appendix 4 Model fits for the microfracture study of Bae et al. 2013

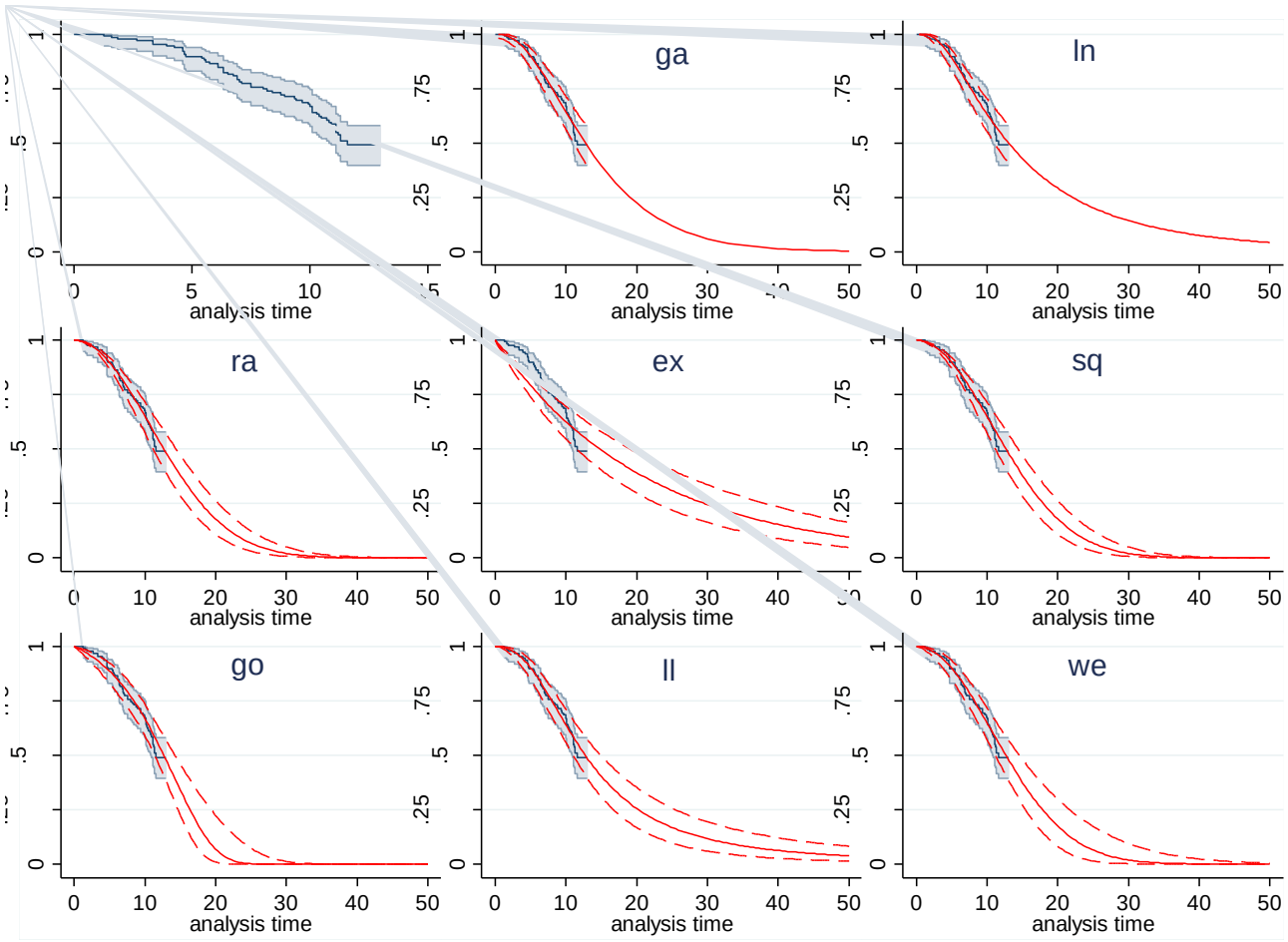


Figure 32 Model fits for Bae study

Analysis time = years. Vertical axis = proportion not failed.

Table 26 Bae study model fits - information criteria.

Model	Obs	ll(model)	df	AIC	BIC
gamma	134	-110.933	3	227.865	236.5585
exponential	134	-125.415	1	252.8301	255.728
weibull	134	-111.216	2	226.4318	232.2275
gompertz	134	-114.11	2	232.2192	238.0148
lognormal	134	-111.698	2	227.3954	233.191
loglogistic	134	-110.807	2	225.6147	231.4104
linear hazard (2 parameters)	134	-111.221	1	224.442	227.3398
linear hazard (1 parameter)	134	-111.221	2	226.442	232.2377

Appendix 5 Models of time to failure included published ACI and MF studies.

This appendix lists information criteria for models used in analyses of reconstructed KM plots and reconstructed IPD. Graphs of model fits for included studies most relevant to the decision problem are presented, arranged by study in alphabetical order. Other Appendices provide model information for the MF study of Bae et al., 2013 [42], Gudas et al., 2012[36], and the unpublished ACTIVE trial.

Data from some studies was sparse and immature (a small proportion of participants experienced an event) and using the specified methods some models and or model 95% CIs could not be computed. Cumulative hazard model tests are available from authors on request

Unless stated otherwise the following abbreviations apply:

bt = bath tub; ex = exponential; ga = gamma; go = Gompertz; ll = loglgistic; ln = lognormal; ra = two parameter linearly increasing hazard model (Rayleigh) ; sq = single parameter linearly increasing hazard model; we = Weibull.

ord = ordinate.

Table 27 AIC and BIC information criteria for parametric models

Bentley et al[11]					
Model	Obs	ll(model)	df	AIC	BIC
gamma	58	-44.3728	3	94.74568	100.927
exponential	58	-46.9174	1	95.83471	97.89515
weibull	58	-46.7082	2	97.4164	101.5373
gompertz	58	-46.8558	2	97.71164	101.8325
lognormal	58	-45.6348	2	95.26963	99.39052
loglogistic	58	-46.3567	2	96.7133	100.8342
Linearly increasing hazard (1 parameter)	58	-49.498	1	100.996	103.0565
Biant et al., 20					
Model	Obs	ll(model)	df	AIC	BIC
gamma	104	-77.5841	3	161.1683	169.1014
exponential	104	-81.5033	1	165.0067	167.6511
Weibull	104	-80.2895	2	164.579	169.8678
gompertz	104	-81.488	2	166.976	172.2648
lognormal	104	-78.3939	2	160.7879	166.0766
loglogistic	104	-79.5402	2	163.0805	168.3693
Linearly increasing hazard (1 parameter)	104	-82.9069	1	167.8137	170.4581
Bath tub	104	-81.443	3	168.886	176.8191
Linearly increasing hazard (2 parameters)	104	-81.443	2	166.886	172.1748
Knutsen et al., 20007 ACI					
Model	Obs	ll(model)	df	AIC	BIC
gamma	40	-28.8468	3	63.69364	68.76028
exponential	40	-29.6877	1	61.37538	63.06426
weibull	40	-29.5975	2	63.1949	66.57266
gompertz	40	-29.6668	2	63.33367	66.71143
lognormal	40	-29.1317	2	62.26343	65.64118
loglogistic	40	-29.4573	2	62.91451	66.29226
Linearly increasing hazard (1 parameter)	40	-31.4127	1	64.82539	66.51427
Knutsen et al., 2007 MF					
Model	Obs	ll(model)	df	AIC	BIC
gamma	40	-25.7202	3	57.44034	62.50698
exponential	40	-27.0267	1	56.05329	57.74217
Weibull	40	-25.7411	2	55.48211	58.85987
gompertz	40	-25.8565	2	55.71308	59.09084
lognormal	40	-25.7855	2	55.57099	58.94875
loglogistic	40	-25.7727	2	55.54536	58.92312
Linearly increasing hazard (2 parameters)	40	-25.801	2	55.60197	58.97973
Linearly increasing hazard (1 parameter)	40	-25.8169	1	53.63372	55.3226
Layton et al[20]					
Model	Obs	ll(model)	df	AIC	BIC
Flexible parametric	3498	-1988.591	2	3981.182	3993.502

gamma	3498	-1972.989	3	3951.978	3970.458
exponential	3498	-2080.367	1	4162.734	4168.894
weibull	3498	-1981.392	2	3966.784	3979.104
gompertz	3498	-1972.5	2	3948.999	3961.319
lognormal	3498	-1981.837	2	3967.675	3979.995
loglogistic	3498	-1988.591	2	3981.182	3993.502
linear hazard one parameter	3498	-1985.295	1	3972.59	3978.75
linear hazard one parameter	3498	-1985.276	2	3974.553	3986.873
Minas et al., 2014 All					
Model	Obs	ll(model)	df	AIC	BIC
exponential	210	-196.368	1	394.7365	398.0836
Weibull	210	-191.79	2	387.5798	394.274
gompertz	210	-185.425	2	374.8509	381.5451
lognormal	210	-187.581	2	379.162	385.8562
loglogistic	210	-190.557	2	385.1139	391.8081
Linearly increasing hazard (1 parameter)	210	-243.436	1	488.8725	492.2196
Minas et al., 2014 previous intervention					
Model	Obs	ll(model)	df	AIC	BIC
gamma	89	-92.1654	3	190.3308	197.7967
exponential	89	-100.147	1	202.2938	204.7824
Weibull	89	-99.7299	2	203.4597	208.437
gompertz	89	-97.3564	2	198.7128	203.69
lognormal	89	-96.9522	2	197.9044	202.8817
loglogistic	89	-98.646	2	201.2921	206.2693
Linearly increasing hazard (1 parameter)	89	-118.007	1	238.0132	240.5019
Minas et al., 2014 no-previous intervention					
Model	Obs	ll(model)	df	AIC	BIC
gamma	121	-87.4531	3	180.9063	189.2936
exponential	121	-94.5668	1	191.1335	193.9293
Weibull	121	-93.769	2	191.5379	197.1295
gompertz	121	-91.2933	2	186.5866	192.1782
lognormal	121	-91.9782	2	187.9563	193.5479
loglogistic	121	-93.3413	2	190.6826	196.2742
Linearly increasing hazard (1 parameter)	121	-110.052	1	222.1033	224.8991
Moseley et al., 2010					
gamma	72	-45.9957	3	97.99145	104.8214
exponential	72	-47.6374	1	97.27483	99.5515
weibull	72	-47.359	2	98.71793	103.2713
gompertz	72	-46.8926	2	97.78513	102.3385
lognormal	72	-46.8112	2	97.62248	102.1758
loglogistic	72	-47.2613	2	98.52252	103.0759
linear hazard (1 parameter)	72	-54.408	1	110.8159	113.0926
Nawaz et al[23]					

Model	Obs	ll(model)	df	AIC	BIC
gamma	827	-568.507	3	1143.014	1157.167
exponential	827	-625.545	1	1253.089	1257.807
Weibull	827	-570.836	2	1145.672	1155.108
gompertz	827	-586.411	2	1176.822	1186.258
lognormal	827	-569.915	2	1143.831	1153.266
loglogistic	827	-568.834	2	1141.668	1151.103
Linearly increasing hazard (2 parameters)	827	-571.708	2	1147.416	1156.851
Linearly increasing hazard (1 parameter)	827	-571.82	1	1145.64	1150.358
Nawaz et al., 2014 previous intervention					
Model	Obs	ll(model)	df	AIC	BIC
gamma	280	-323.345	3	652.69	663.5944
exponential	280	-360.259	1	722.5175	726.1522
weibull	280	-335.845	2	675.6899	682.9595
gompertz	280	-351.191	2	706.3822	713.6518
lognormal	280	-323.529	2	651.058	658.3276
loglogistic	280	-323.9	2	651.7998	659.0694
Linearly increasing hazard (1 parameter)	280	-348.764	1	699.5281	703.1629
bath tub	280	-344.046	3	694.091	704.9954
Linearly increasing hazard (2 parameters)	280	-344.046	2	692.091	699.3606
Nawaz et al., 2014 no previous intervention					
Model	Obs	ll(model)	df	AIC	BIC
gamma	547	-404.093	3	814.186	827.0994
exponential	547	-422.594	1	847.1882	851.4926
weibull	547	-413.556	2	831.1128	839.7217
gompertz	547	-421.083	2	846.1666	854.7755
lognormal	547	-405.991	2	815.9812	824.5901
loglogistic	547	-410.462	2	824.9231	833.532
Bath tub	547	-418.881	3	843.7628	856.6761
Linearly increasing hazard (2 parameters)	547	-418.881	2	841.7628	850.3717
Linearly increasing hazard (1 parameter)	547	-423.034	1	848.0674	852.3718
Nawaz et al., 2014 lateral femoral site					
Model	Obs	ll(model)	df	AIC	BIC
gamma	109	-80.7189	3	167.4378	175.5118
exponential	109	-84.7776	1	171.5553	174.2466
Weibull	109	-83.4963	2	170.9926	176.3753
gompertz	109	-84.7494	2	173.4988	178.8815
lognormal	109	-81.5869	2	167.1738	172.5565
loglogistic	109	-82.759	2	169.5179	174.9006
Linearly increasing hazard (1 parameters)	109	-86.1576	1	174.3151	177.0065
Linearly increasing hazard (2 parameter)	109	-84.6778	2	173.3557	178.7384
Nawaz et al., 2014 medial femoral site					
Model	Obs	ll(model)	df	AIC	BIC
gamma	421	-466.36	3	938.719	950.8469

exponential	421	-489.691	1	981.3818	985.4245
weibull	421	-478.693	2	961.3867	969.4719
gompertz	421	-487.87	2	979.7396	987.8249
lognormal	421	-467.487	2	938.973	947.0583
loglogistic	421	-470.581	2	945.1612	953.2465
Bath tub	421	-486.252	3	978.5033	990.6312
Linearly increasing hazard (1 parameter)	421	-501.922	1	1005.844	1009.887
Linearly increasing hazard (2 parameters)	421	-486.252	2	976.5033	984.5886
Nawaz et al., 2014 multisite					
Model	Obs	ll(model)	df	AIC	BIC
gamma	47	-43.0205	3	92.04091	97.59135
exponential	47	-49.4276	1	100.8552	102.7053
weibull	47	-44.5392	2	93.07841	96.77871
gompertz	47	-46.4715	2	96.94301	100.6433
lognormal	47	-43.2675	2	90.5349	94.2352
loglogistic	47	-43.7604	2	91.52073	95.22102
Linearly increasing hazard (1 parameter)	47	-44.5599	1	91.11976	92.96991
Linearly increasing hazard (2 parameters)	47	-44.0869	2	92.17384	95.87413
Nawaz et al., 2014 [23] patella site					
Model	Obs	ll(model)	df	AIC	BIC
gamma	200	-213.659	3	433.3189	443.2138
exponential	200	-227.676	1	457.3519	460.6502
weibull	200	-216.182	2	436.3644	442.961
gompertz	200	-221.612	2	447.2244	453.821
lognormal	200	-213.703	2	431.4064	438.003
loglogistic	200	-213.828	2	431.6568	438.2534
Linearly increasing hazard (2 parameters)	200	-218.561	2	441.1217	447.7183
Linearly increasing hazard (1 parameter)	200	-220.296	1	442.5924	445.8907
Nawaz et al., 2014 trochlea site					
Model	Obs	ll(model)	df	AIC	BIC
gamma	50	-46.1589	3	98.31787	104.0539
exponential	50	-48.5806	1	99.16116	101.0732
weibull	50	-46.3142	2	96.62834	100.4524
gompertz	50	-47.1127	2	98.22545	102.0495
lognormal	50	-46.2374	2	96.47485	100.2989
loglogistic	50	-46.1139	2	96.2278	100.0518
Linearly increasing hazard (1 parameter)	50	-46.8221	1	95.64415	97.55618
Linearly increasing hazard (2 parameters)	50	-46.5753	2	97.15064	100.9747
Niemeyer et al., 2014[25]					
Model	Obs	ll(model)	df	AIC	BIC
gamma	70	-61.0638	3	128.1277	134.8732
exponential	70	-60.8876	1	123.7751	126.0236
weibull	70	-60.8874	2	125.7747	130.2717
gompertz	70	-60.8557	2	125.7113	130.2083

lognormal	70	-60.0888	2	124.1775	128.6745
loglogistic	70	-60.7415	2	125.4829	129.9799
Linearly increasing hazard (1 parameter)	70	-68.8165	1	139.6329	141.8814
Linearly increasing hazard (2 parameters)	70	-60.8622	2	125.7245	130.2215
Vanlauwe et al., 2011 ACI[1]					
Model	Obs	ll(model)	df	AIC	BIC
gamma	51	-21.6794	3	49.35883	55.1543
exponential	51	-23.3598	1	48.71968	50.65151
weibull	51	-21.681	2	47.3619	51.22555
gompertz	51	-21.8389	2	47.67779	51.54144
lognormal	51	-21.8216	2	47.6432	51.50685
loglogistic	51	-21.6851	2	47.3701	51.23375
Linearly increasing hazard (1 parameter)	51	-21.6856	1	45.37118	47.30301
Linearly increasing hazard (2 parameters)	51	-21.6531	2	47.30627	51.16992
Vanlauwe et al., 2011 MF					
Model	Obs	ll(model)	df	AIC	BIC
gamma	61	-32.4298	3	70.85961	77.19223
exponential	61	-35.7444	1	73.48888	75.59975
weibull	61	-35.628	2	75.25597	79.47772
gompertz	61	-35.6081	2	75.21612	79.43787
lognormal	61	-34.7726	2	73.54515	77.76689
loglogistic	61	-35.4313	2	74.86256	79.08431
Linearly increasing hazard (1 parameter)	61	-37.6677	1	77.3354	79.44627
Linearly increasing hazard (2 parameters)	61	-35.3329	2	74.66589	78.88763
Saris et al., 2009 ACI					
Model	Obs	ll(model)	df	AIC	BIC
gamma	61	-22.6833	3	51.36665	57.69927
exponential	61	-25.351	1	52.70196	54.81284
weibull	61	-23.947	2	51.89407	56.11582
gompertz	61	-24.5998	2	53.19964	57.42138
lognormal	61	-23.5357	2	51.07138	55.29313
loglogistic	61	-23.8799	2	51.75988	55.98163
Linearly increasing hazard (1 parameters)	61	-23.9471	1	49.89419	52.00507
Model	Obs	ll(model)	df	AIC	BIC
gamma					
exponential					
weibull					
gompertz					
lognormal					
loglogistic					
Linearly increasing hazard (1 parameter)					
bath tub					

Linearly increasing hazard (2 parameters)					

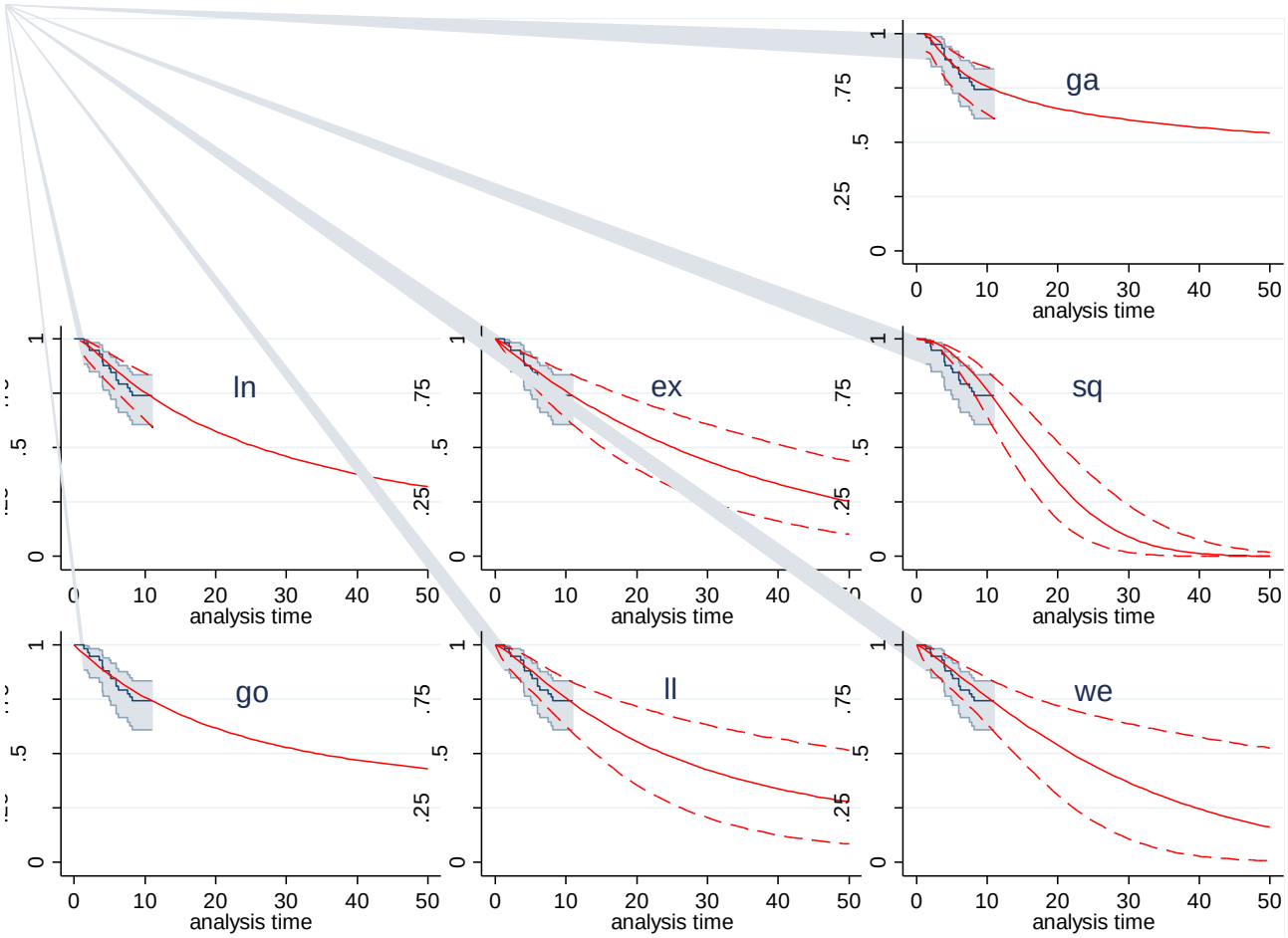
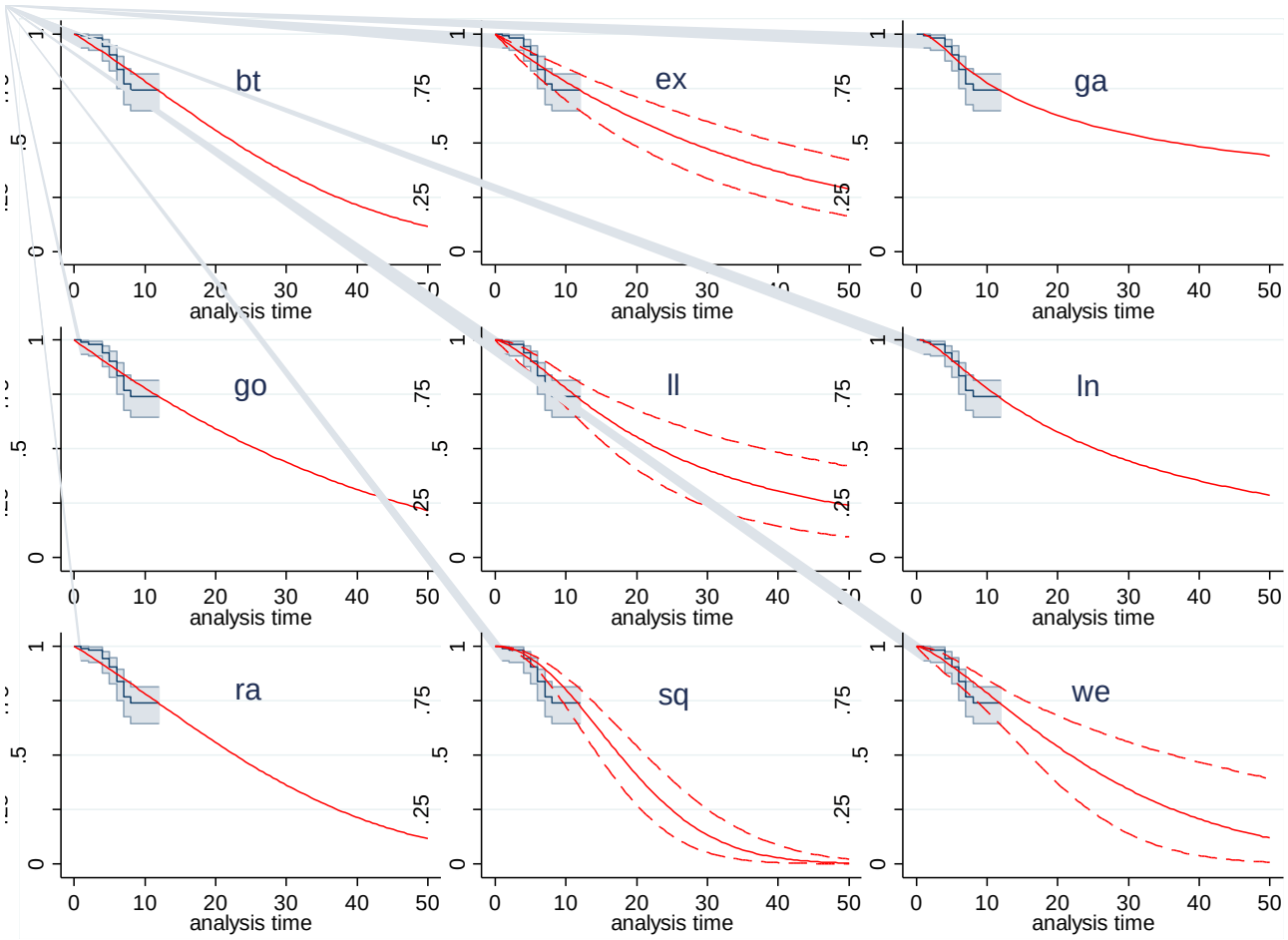


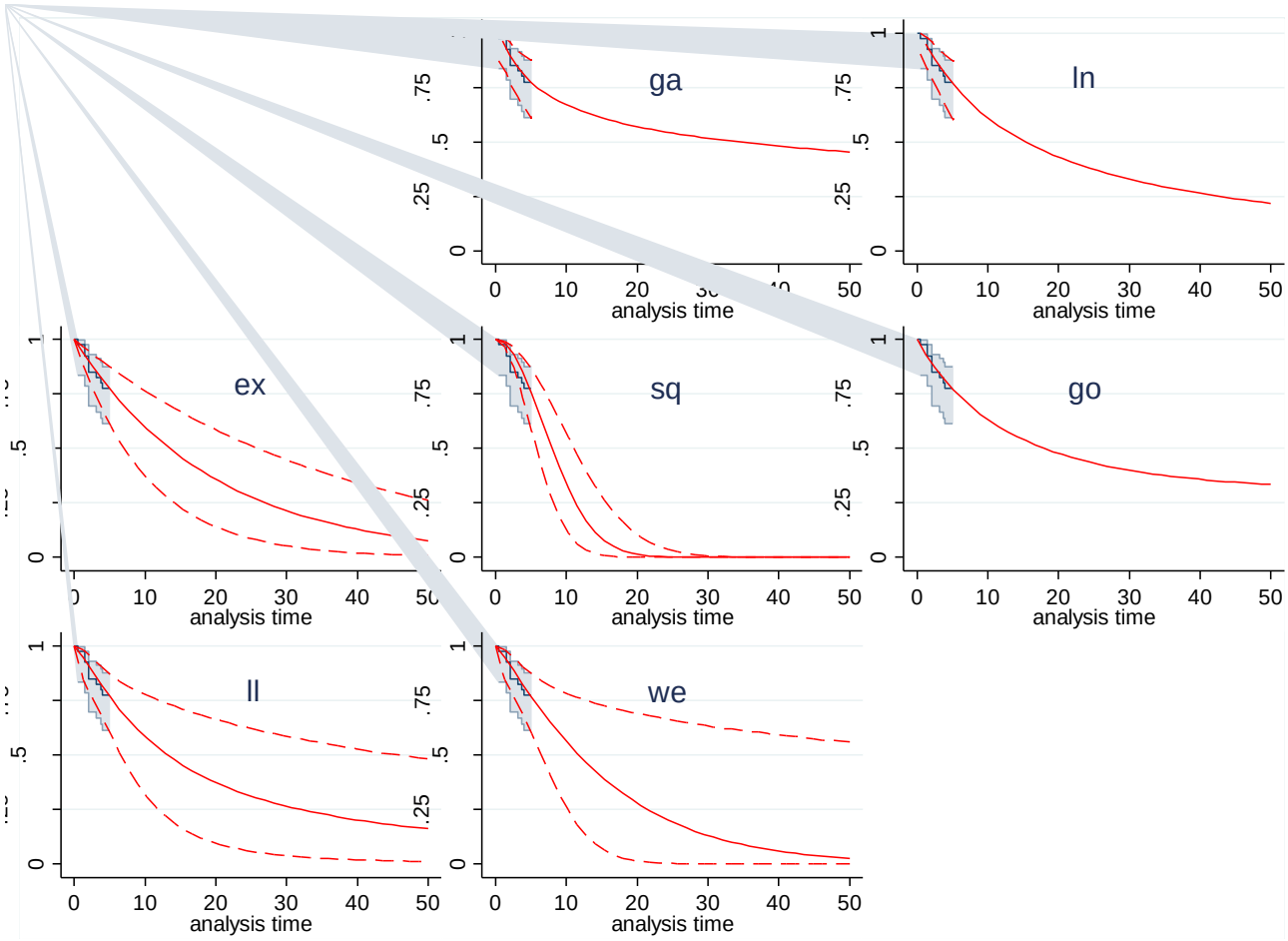
Figure 33 Bentley et al., 2012 ACI arm model fits

Analysis time = years. Vertical axis = proportion not failed.



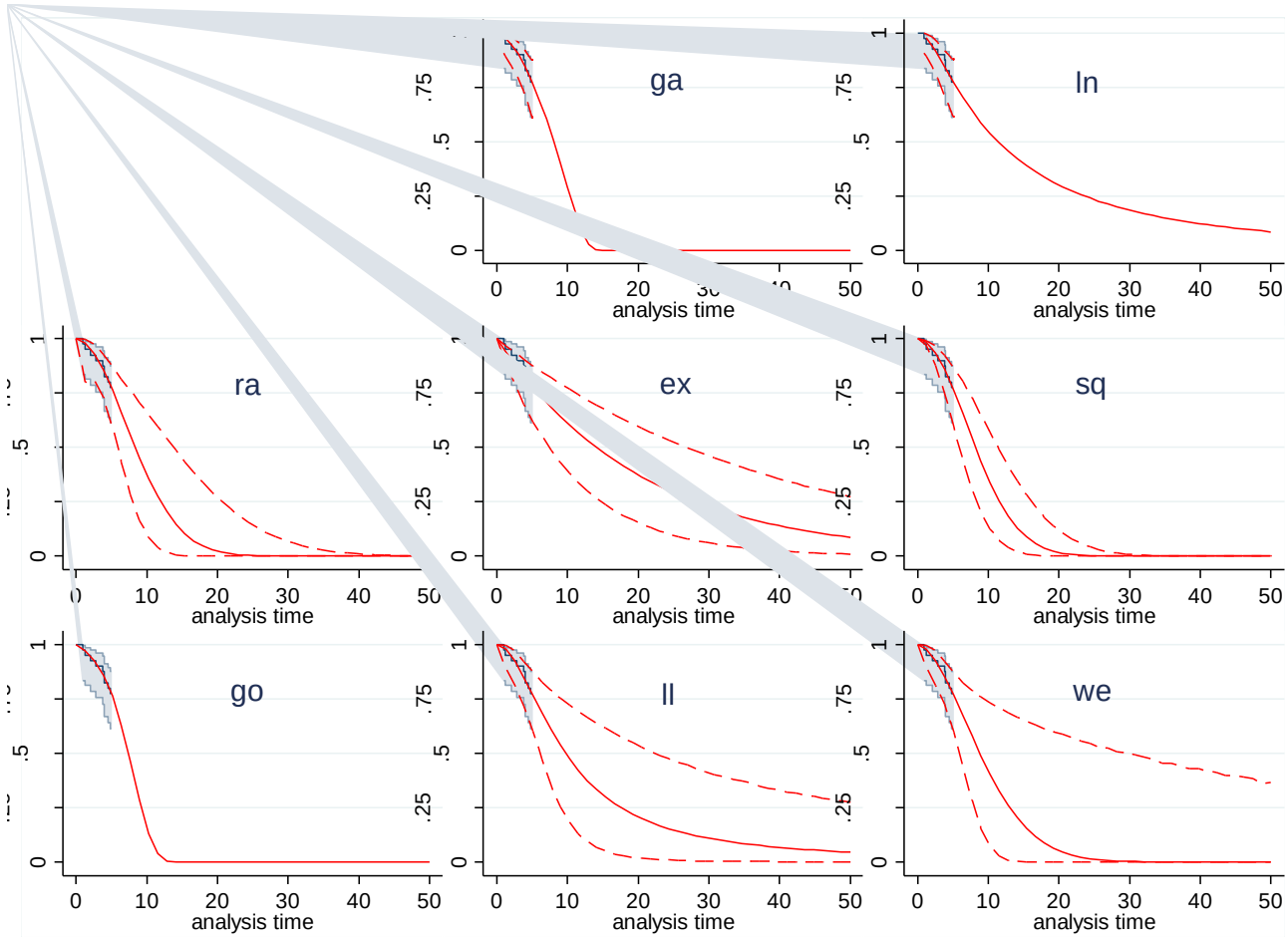
Analysis time = years. Vertical axis = proportion not failed.

Figure 34 Biant et al., 2014 ACI model fits



Analysis time = years. Vertical axis = proportion not failed.

Figure 35 Knutsen et al., 2007[19] model fits ACI arm



Analysis time = years. Vertical axis = proportion not failed.

Figure 36. Knutsen et al., 2007 model fits MF arm

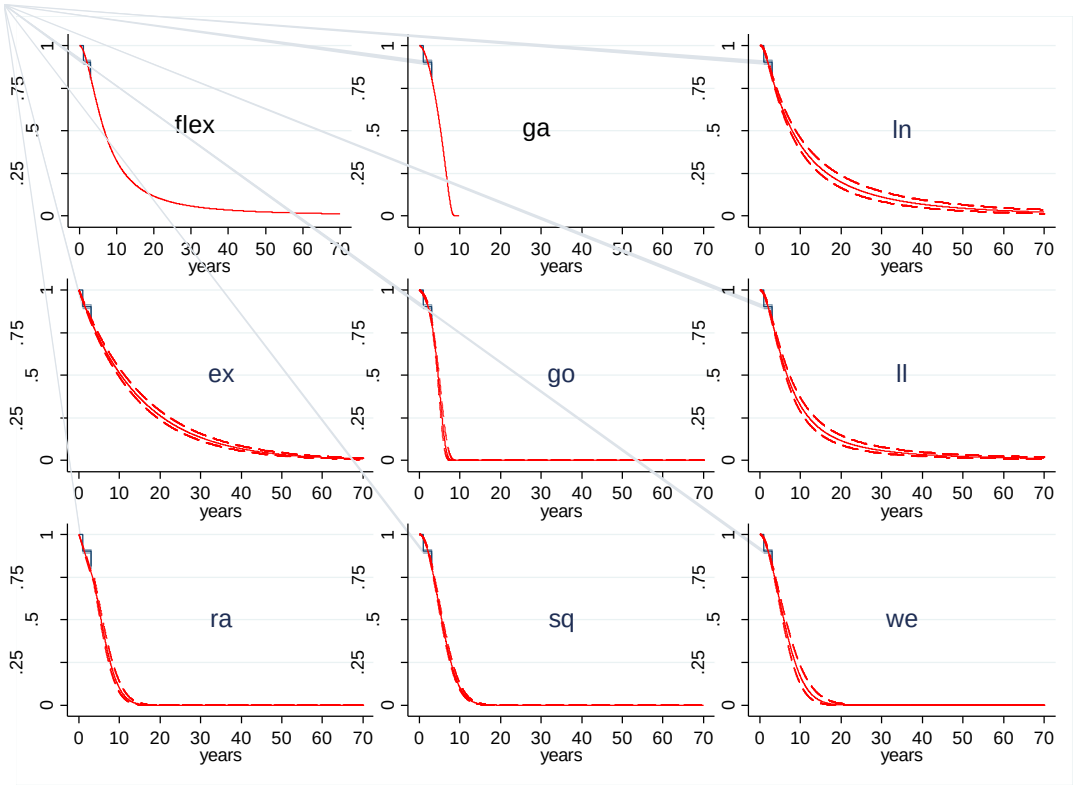
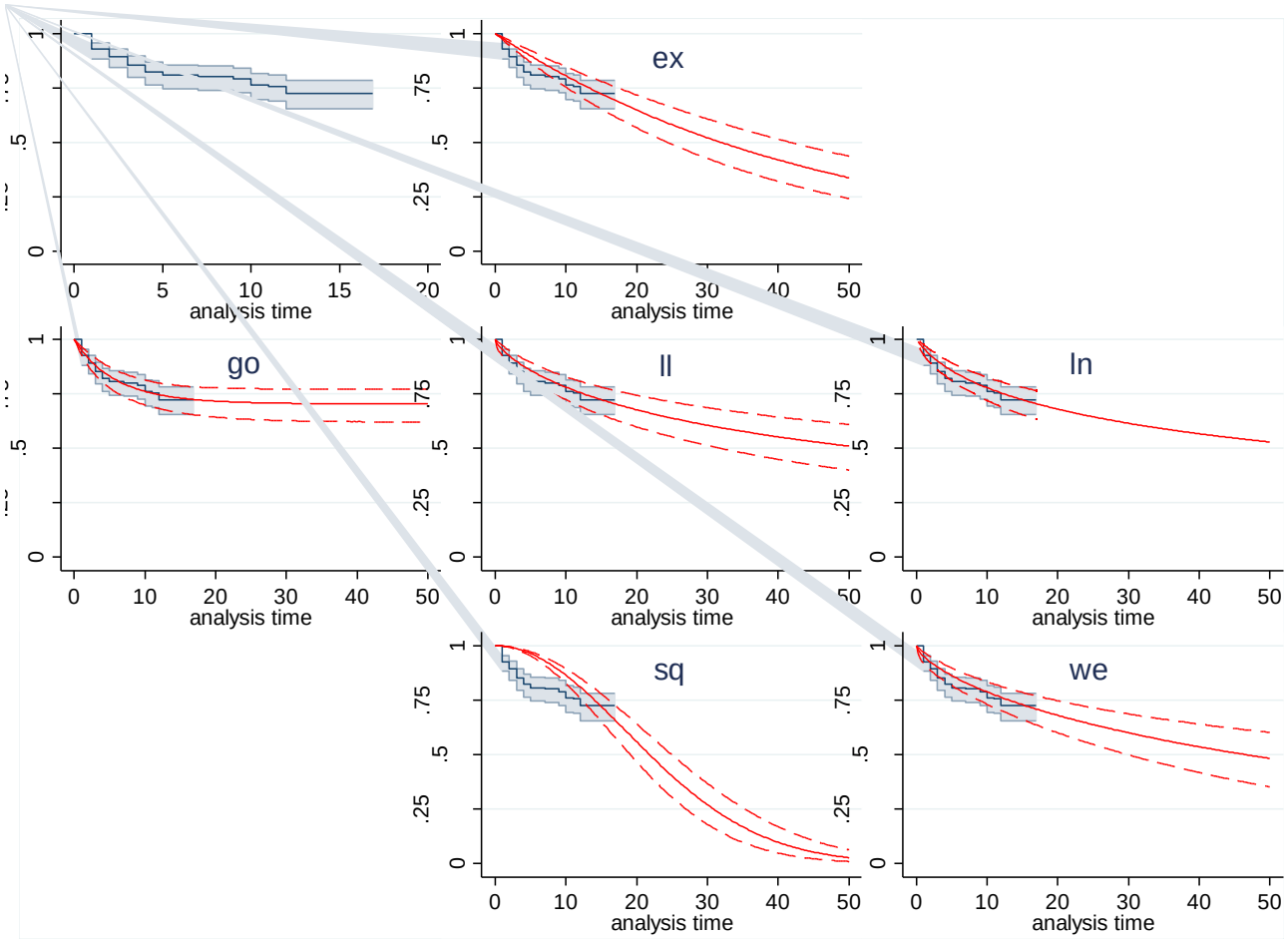
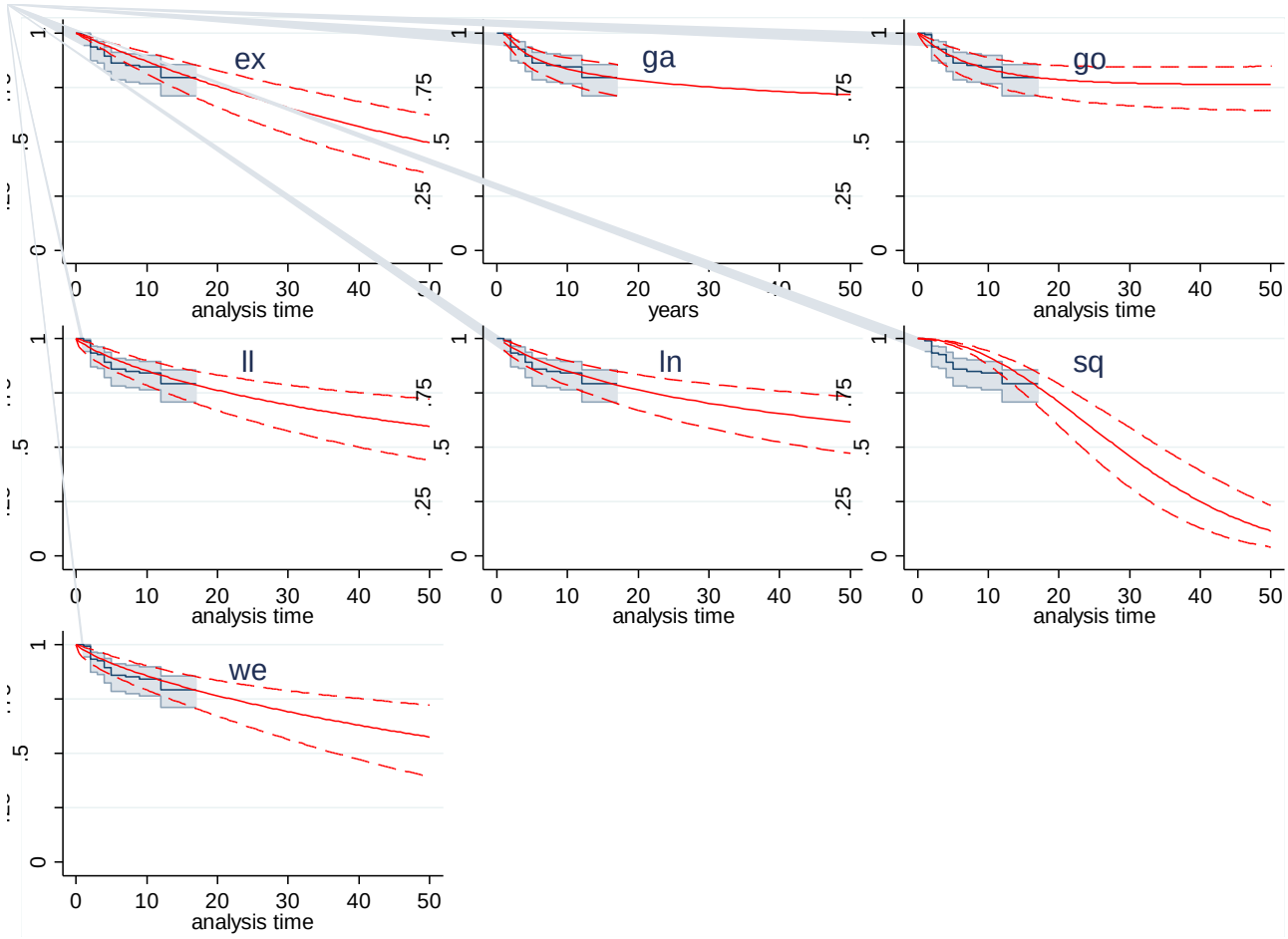


Figure 37. Layton et al., 2015 model fits MF



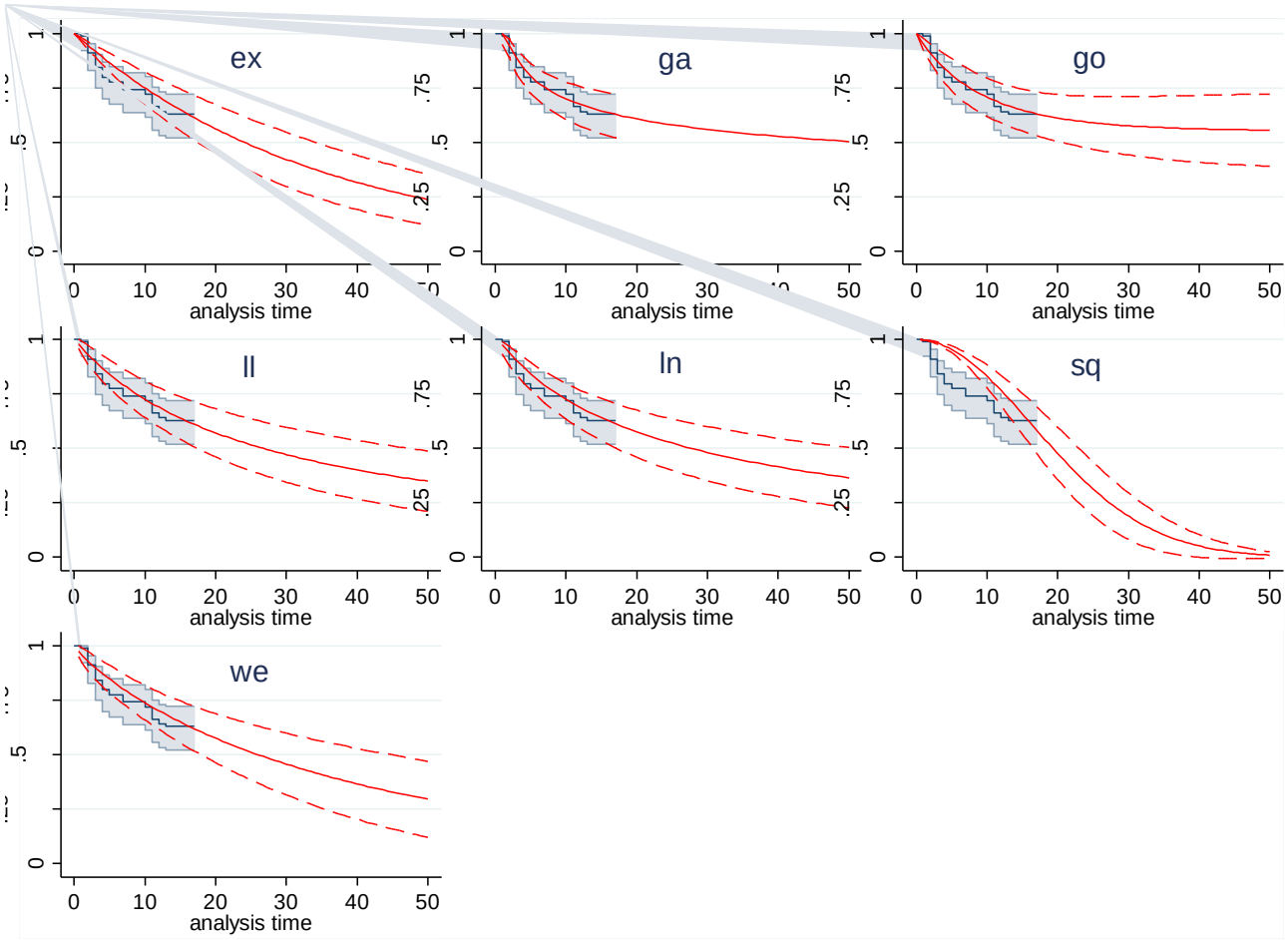
Analysis time = years. Vertical axis = proportion not failed.

Figure 38. Minas et al. 2014 model fits ACI



Analysis time = years. Vertical axis = proportion not failed.

Figure 39 Minas et al. 2014 model fits ACI no previous intervention



Analysis time = years. Vertical axis = proportion not failed.

Figure 40 Minas et al. 2014 model fits ACI previous intervention

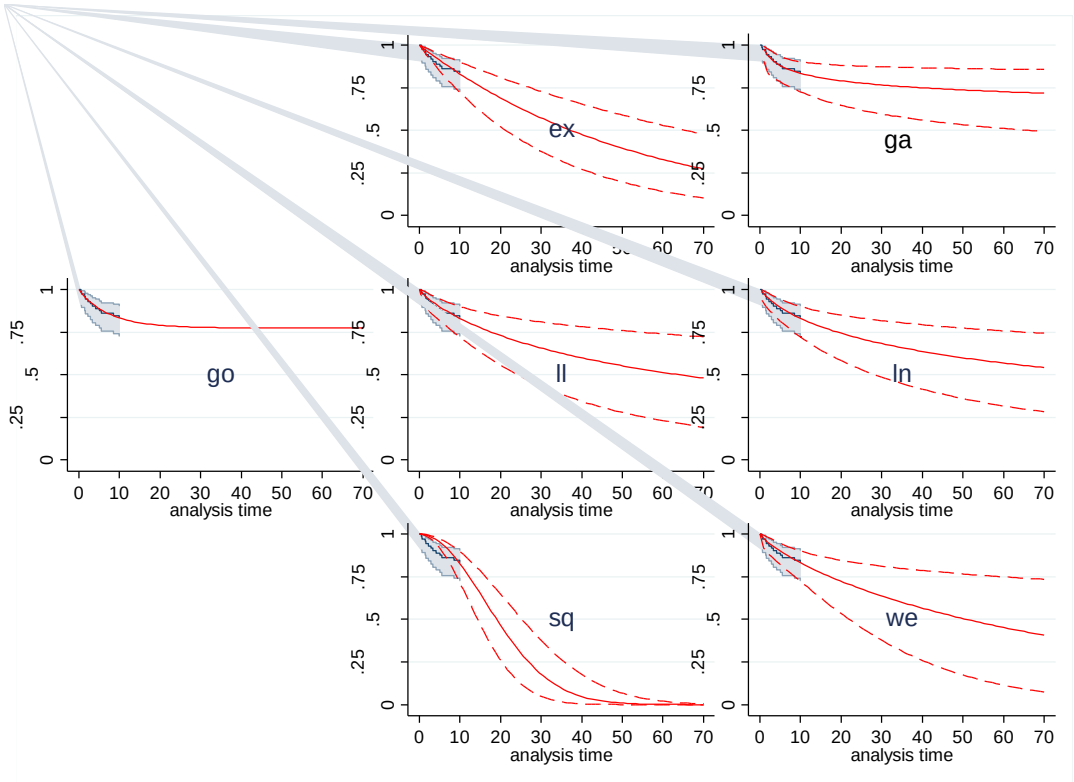
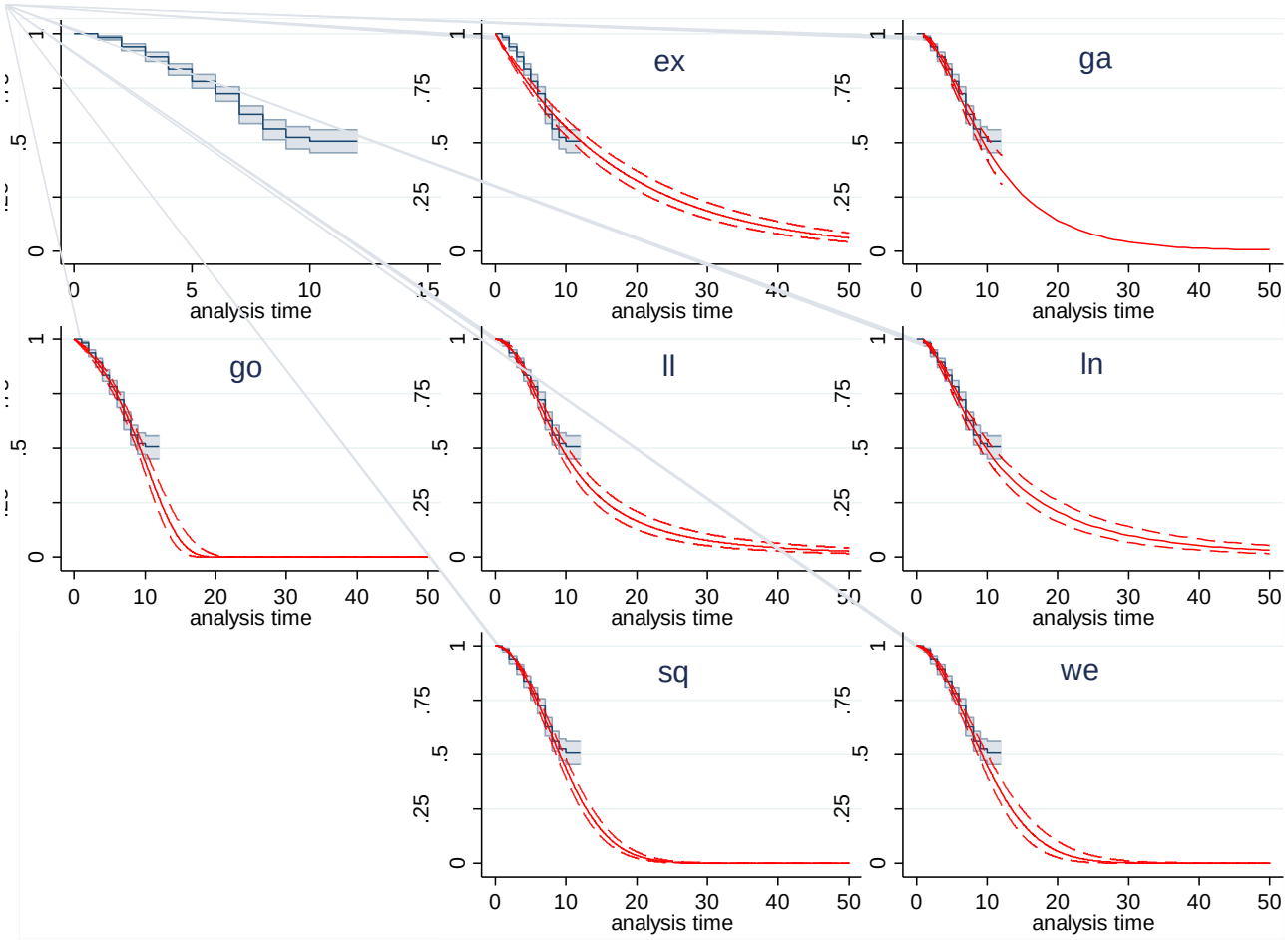
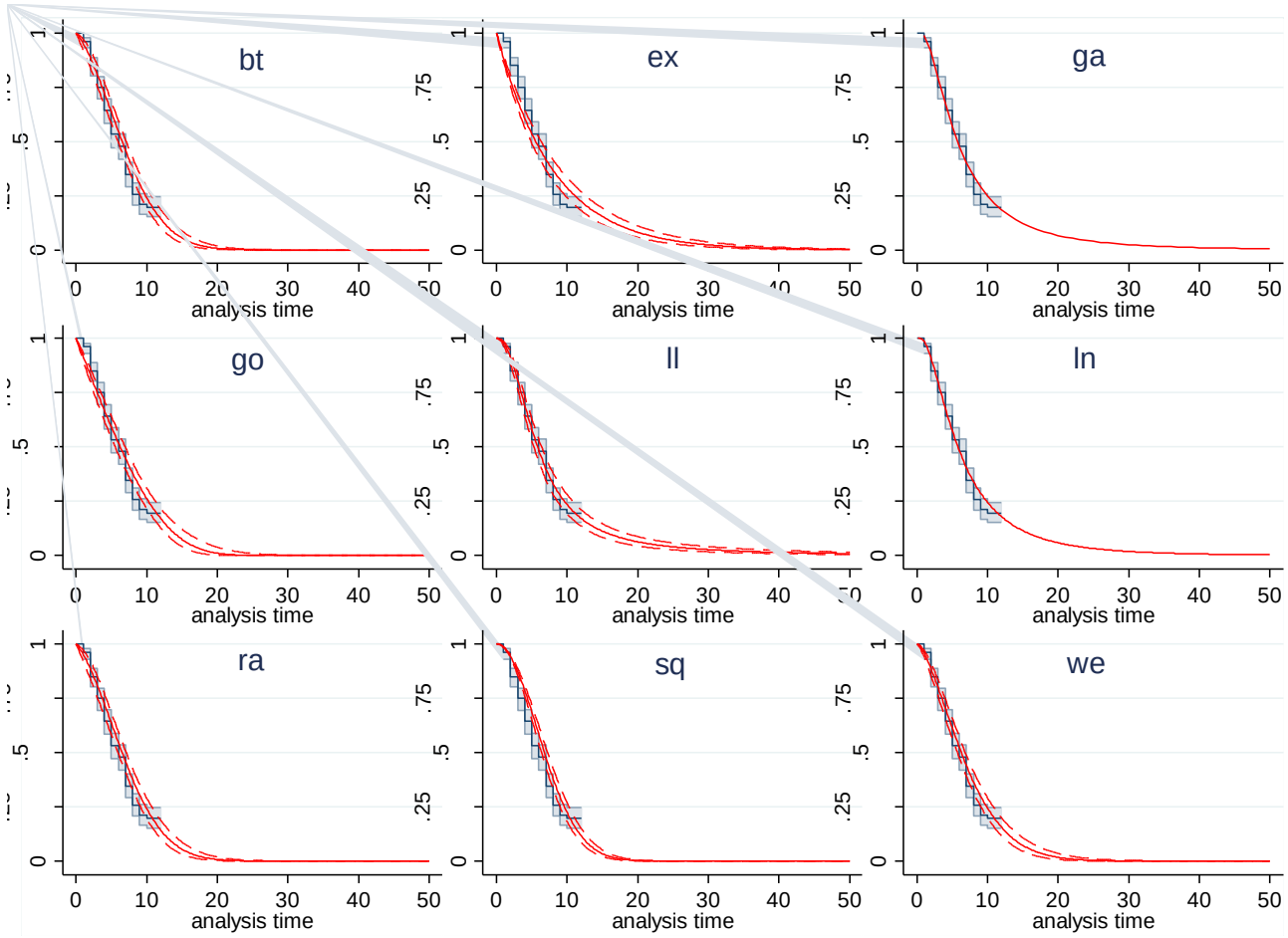


Figure 41 Moseley et al. 2010 model fits ACI



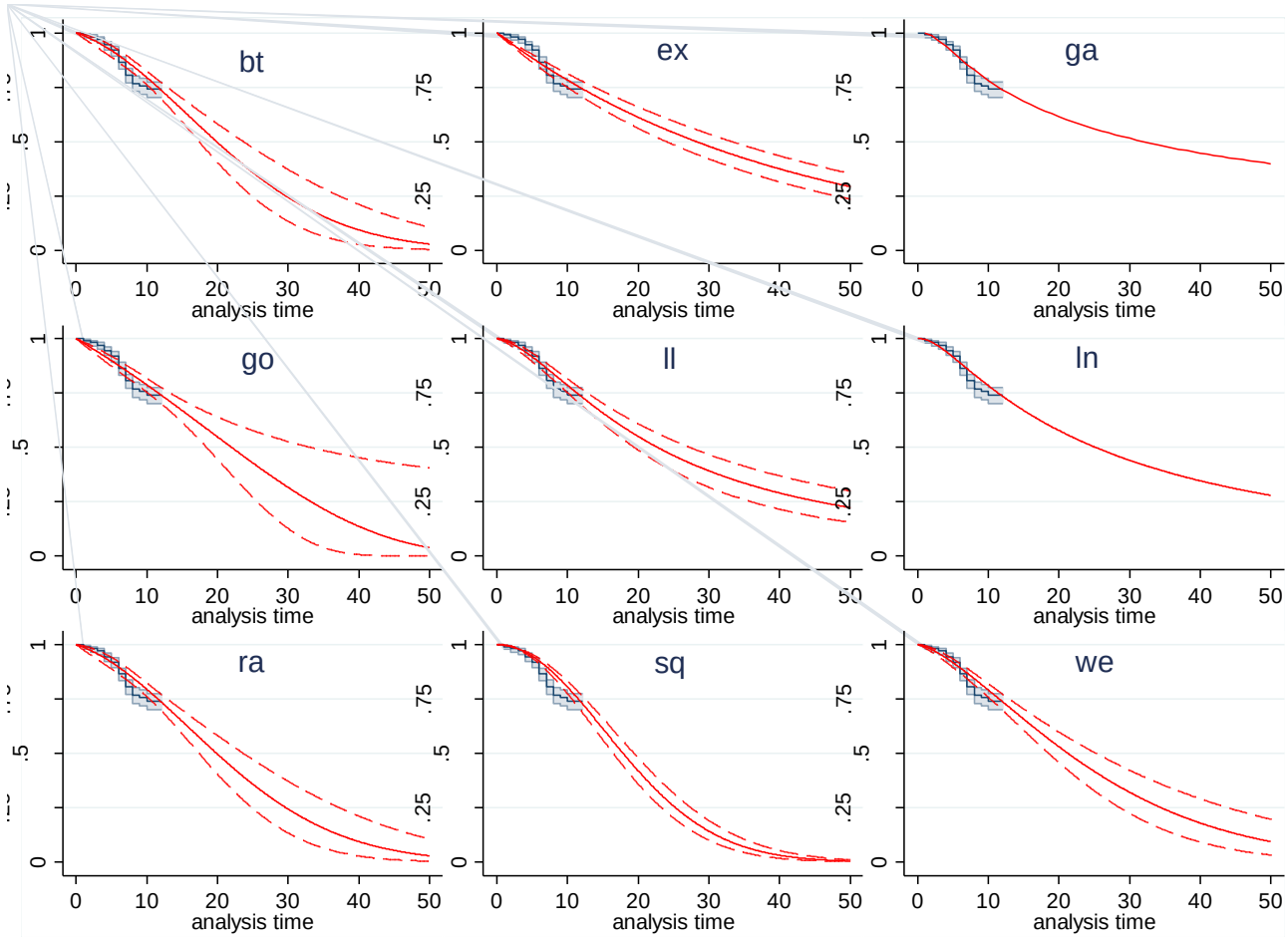
Analysis time = years. Vertical axis = proportion not failed.

Figure 42 Nawaz et al. 2014 model fits ACI whole cohort



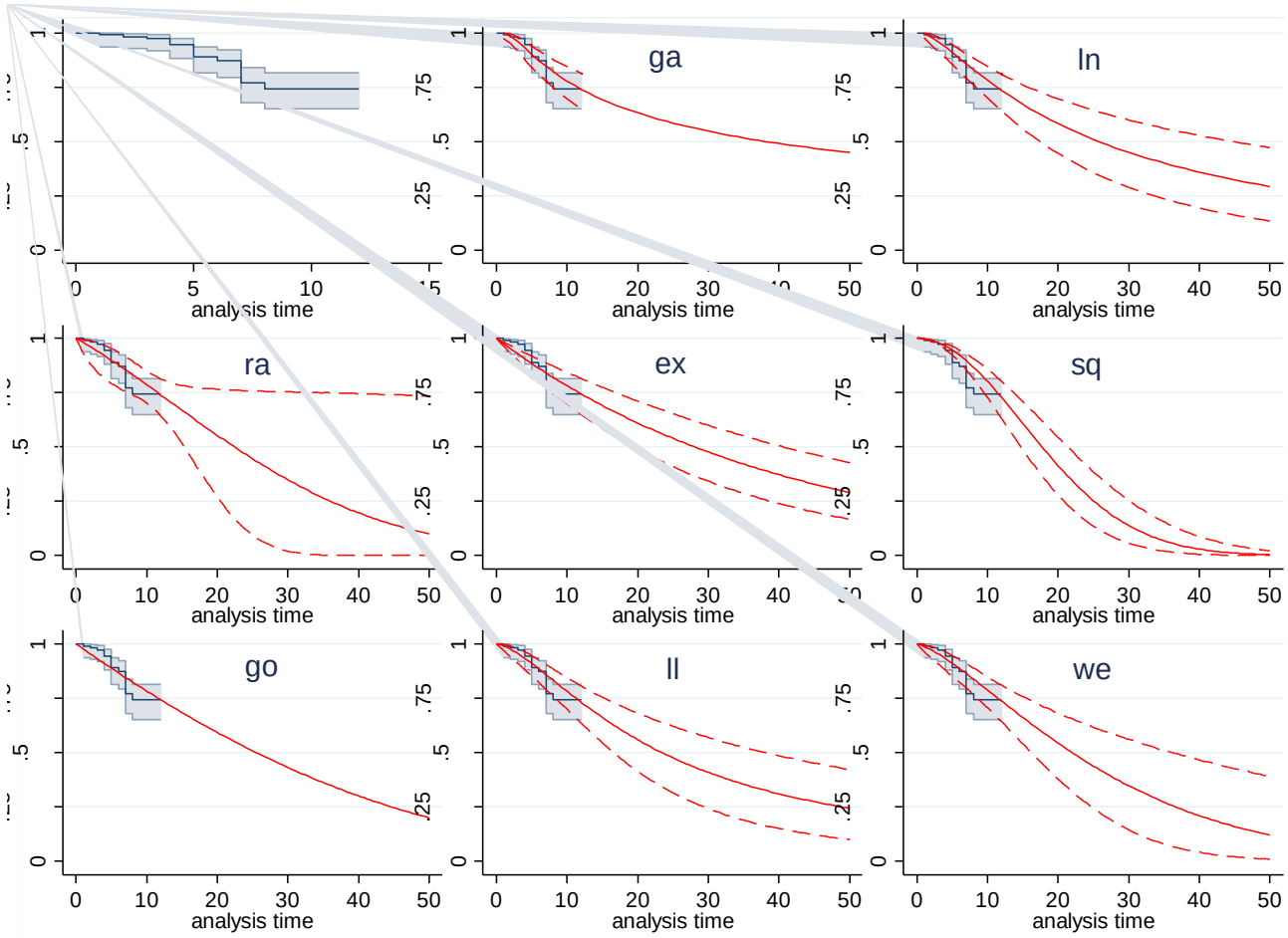
Analysis time = years. Vertical axis = proportion not failed.

Figure 43 Nawaz et al model fits ACI previous intervention



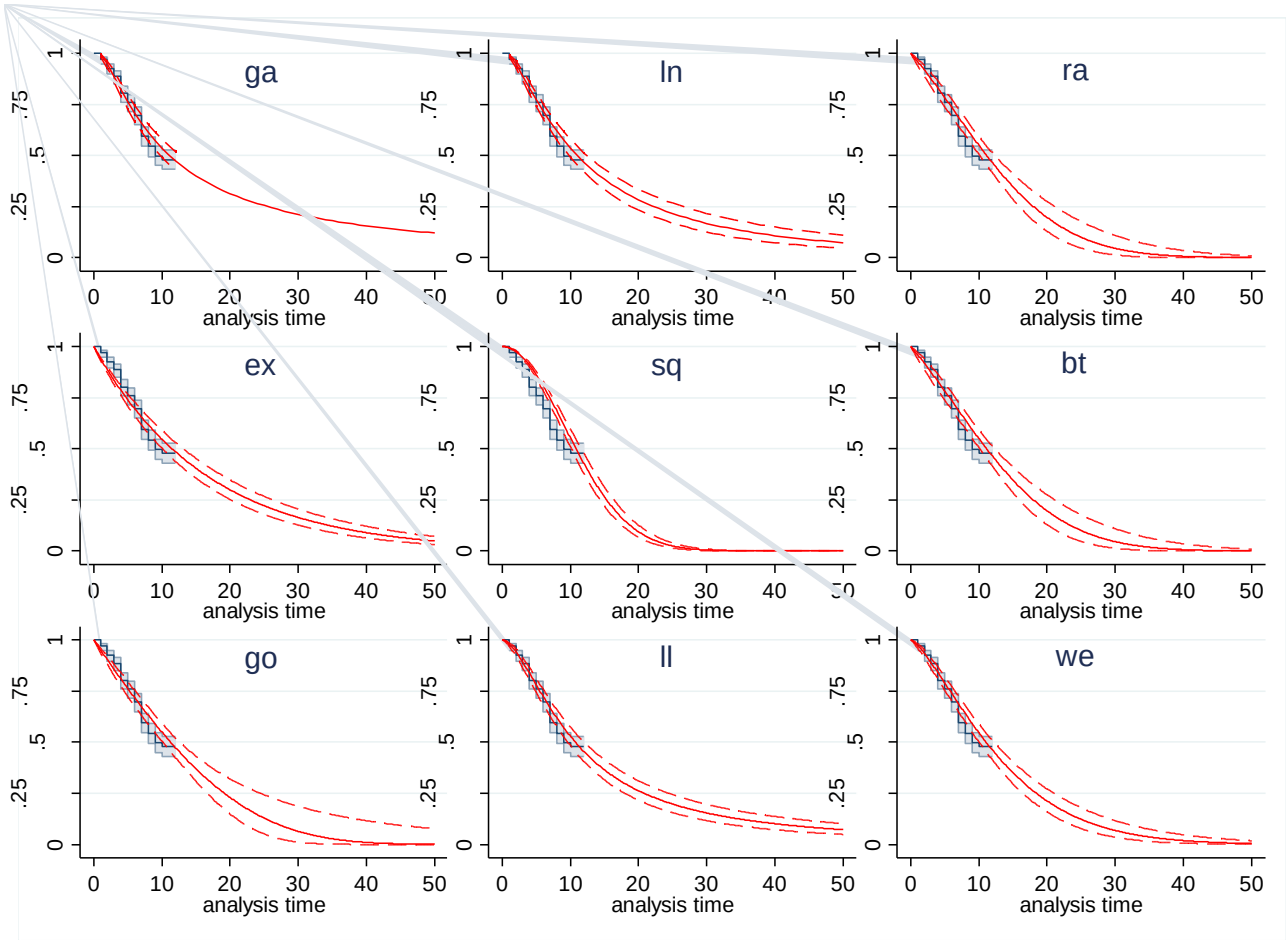
Analysis time = years. Vertical axis = proportion not failed.

Figure 44 Nawaz et al, 2014 model fits ACI no previous intervention



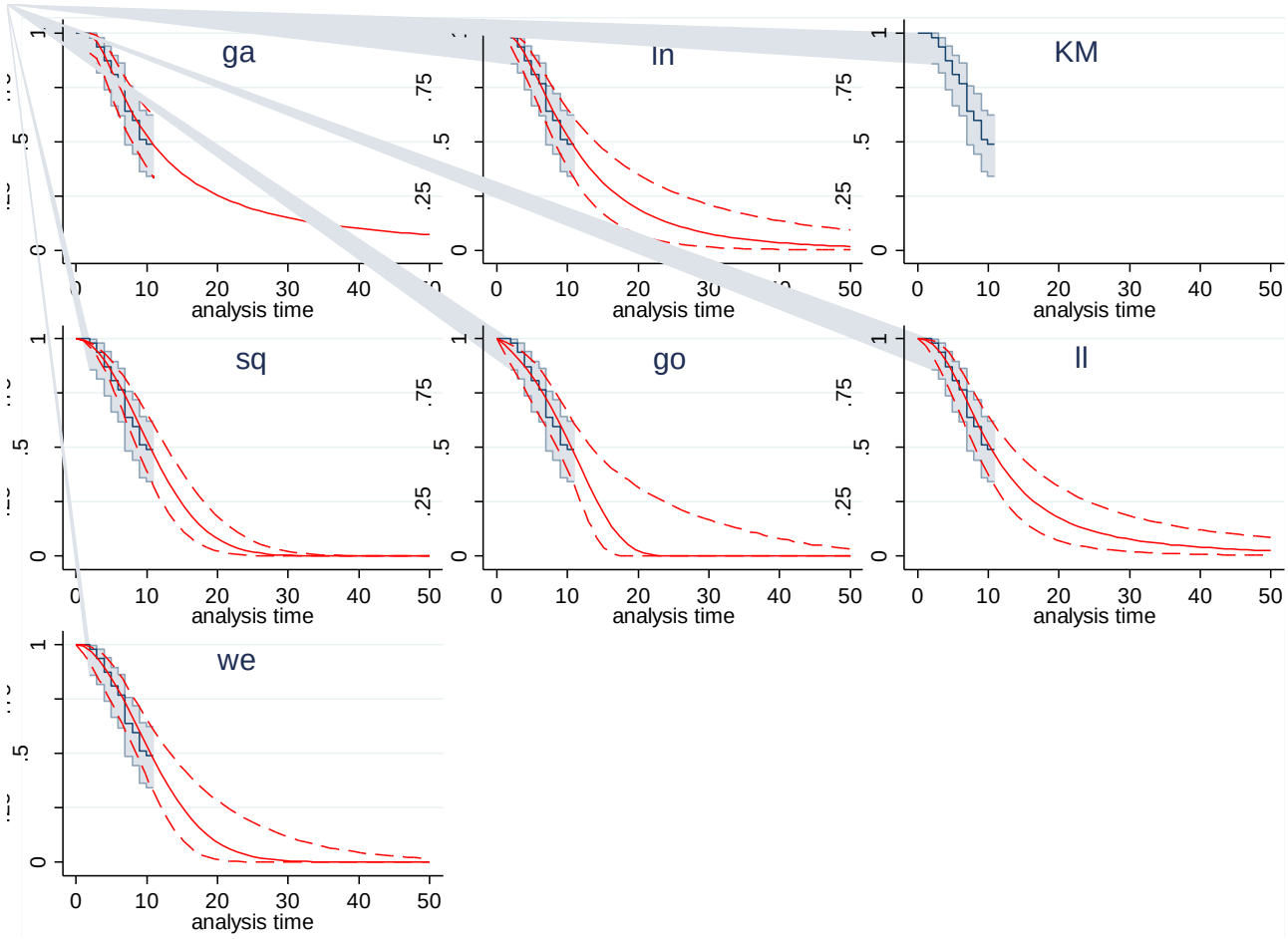
Analysis time = years. Vertical axis = proportion not failed.

Figure 45 Nawaz et al. 2014 model fits ACI lateral femoral site



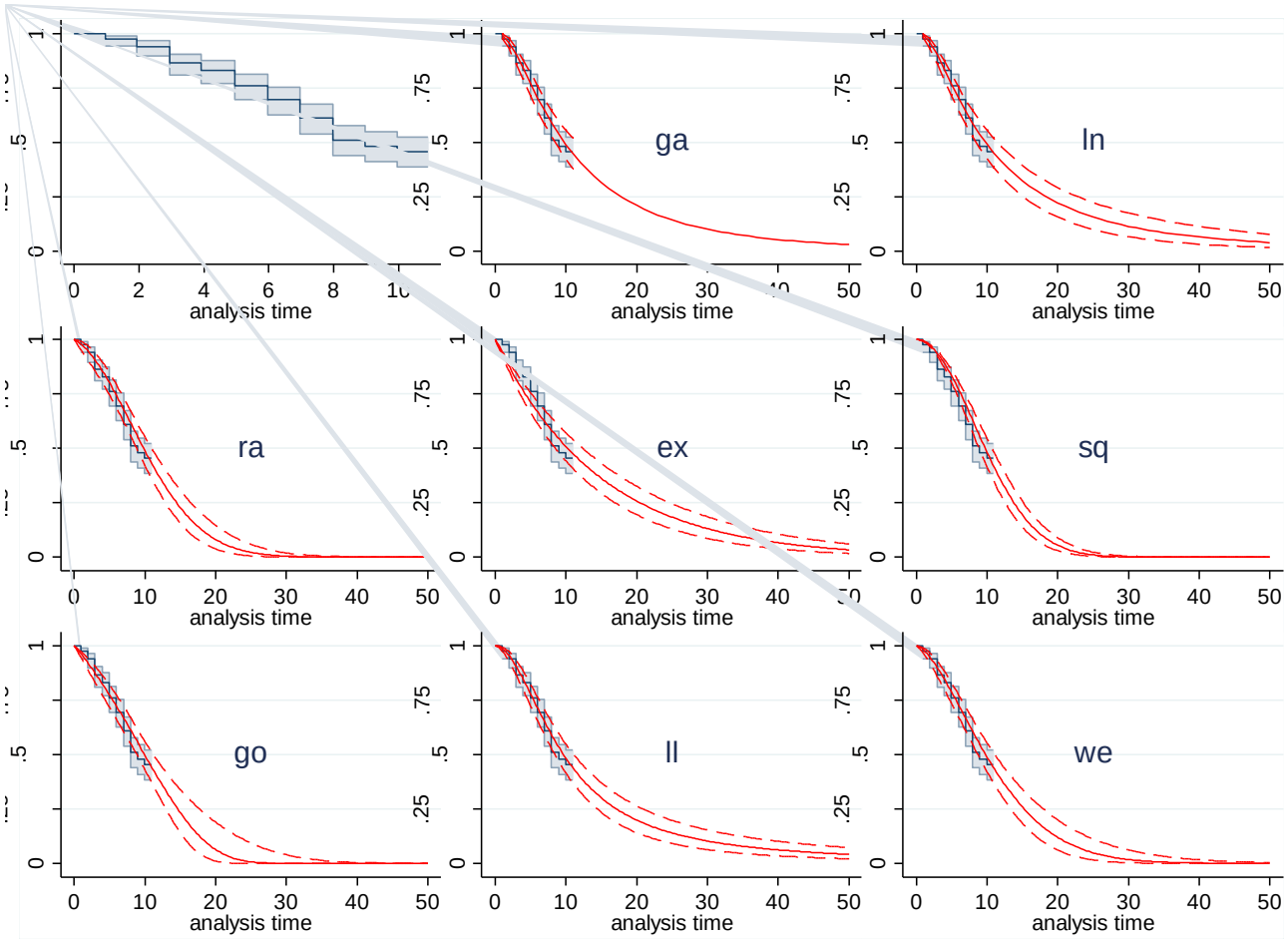
Analysis time = years. Vertical axis = proportion not failed.

Figure 46 Nawaz et al., 2014 model fits ACI lateral femoral site



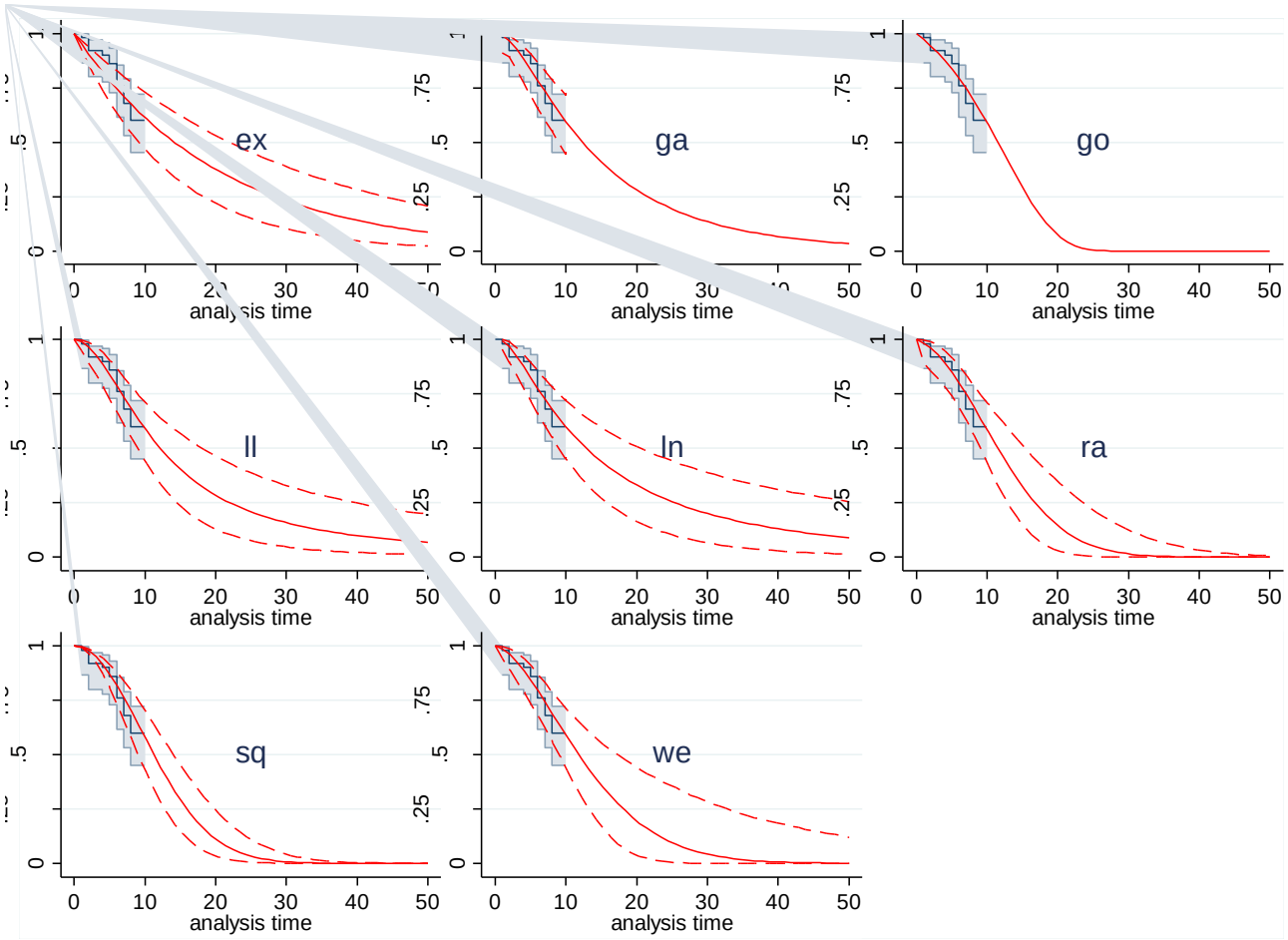
Analysis time = years. Vertical axis = proportion not failed.

Figure 47 Nawaz et al., 2014 model fits ACI multi site



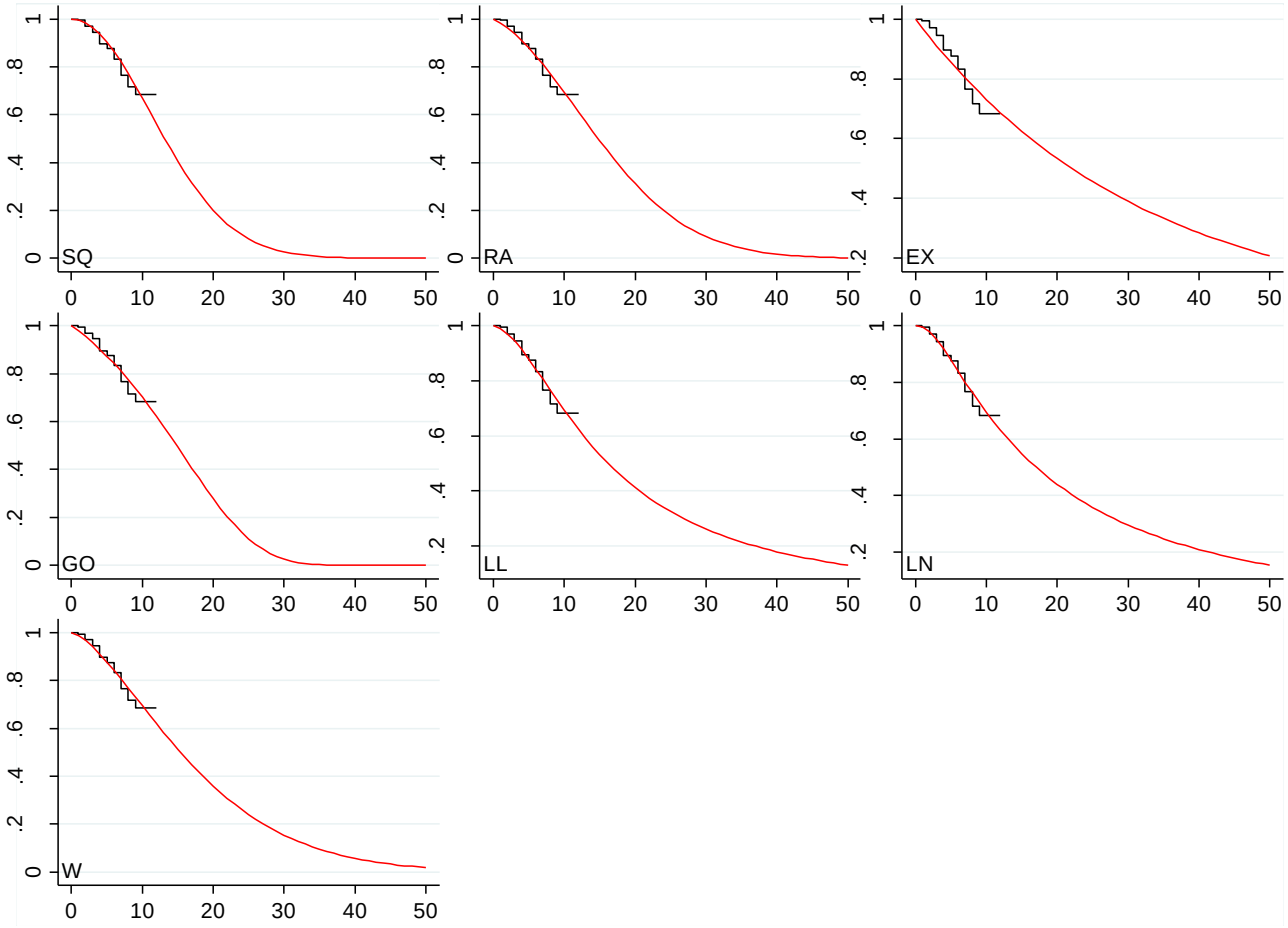
Analysis time = years. Vertical axis = proportion not failed.

Figure 48 Nawaz et al., 2014 model fits ACI patella site



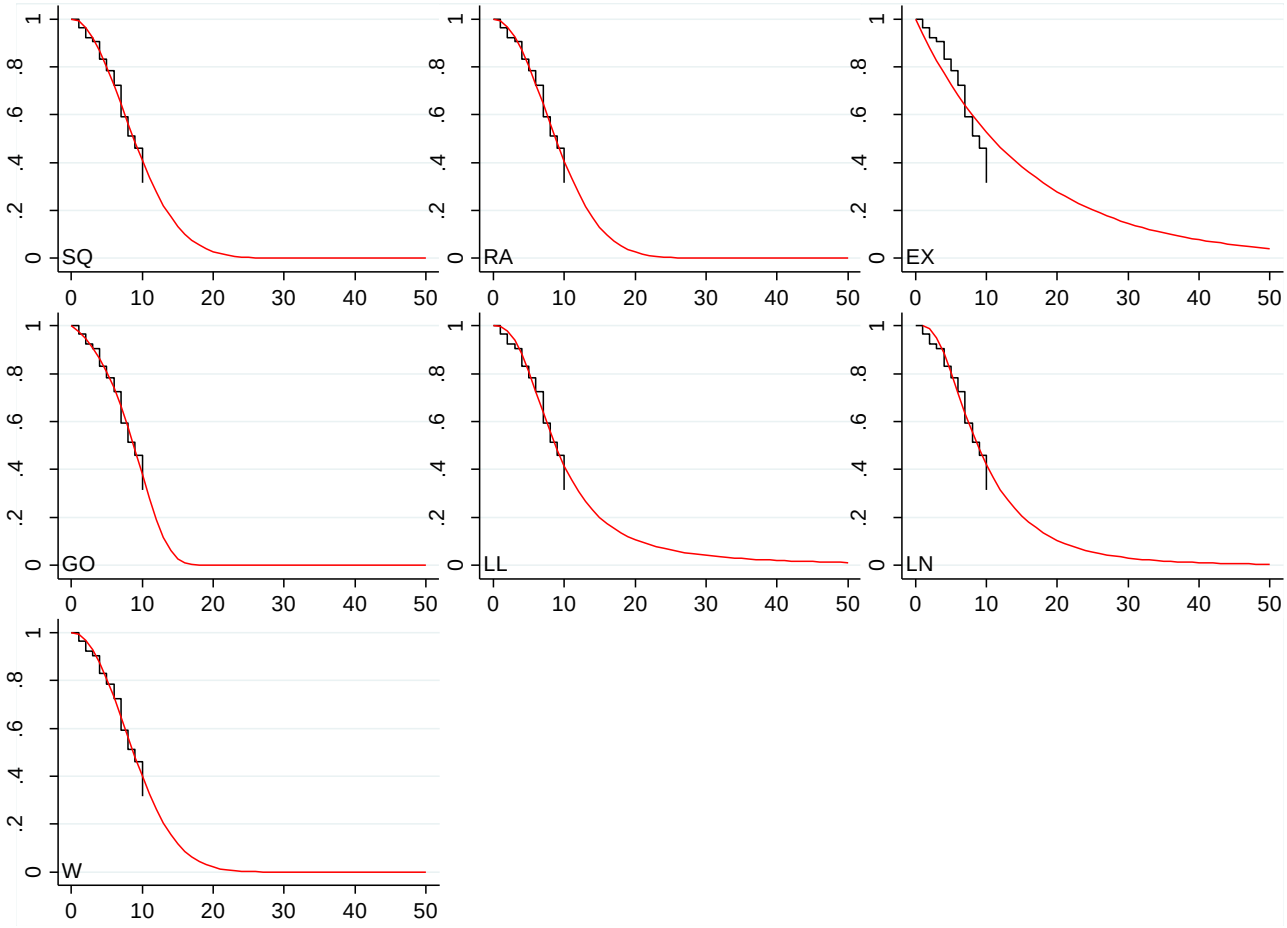
Analysis time = years. Vertical axis = proportion not failed.

Figure 49 Nawaz et al. 2014 model fits ACI trochlea site



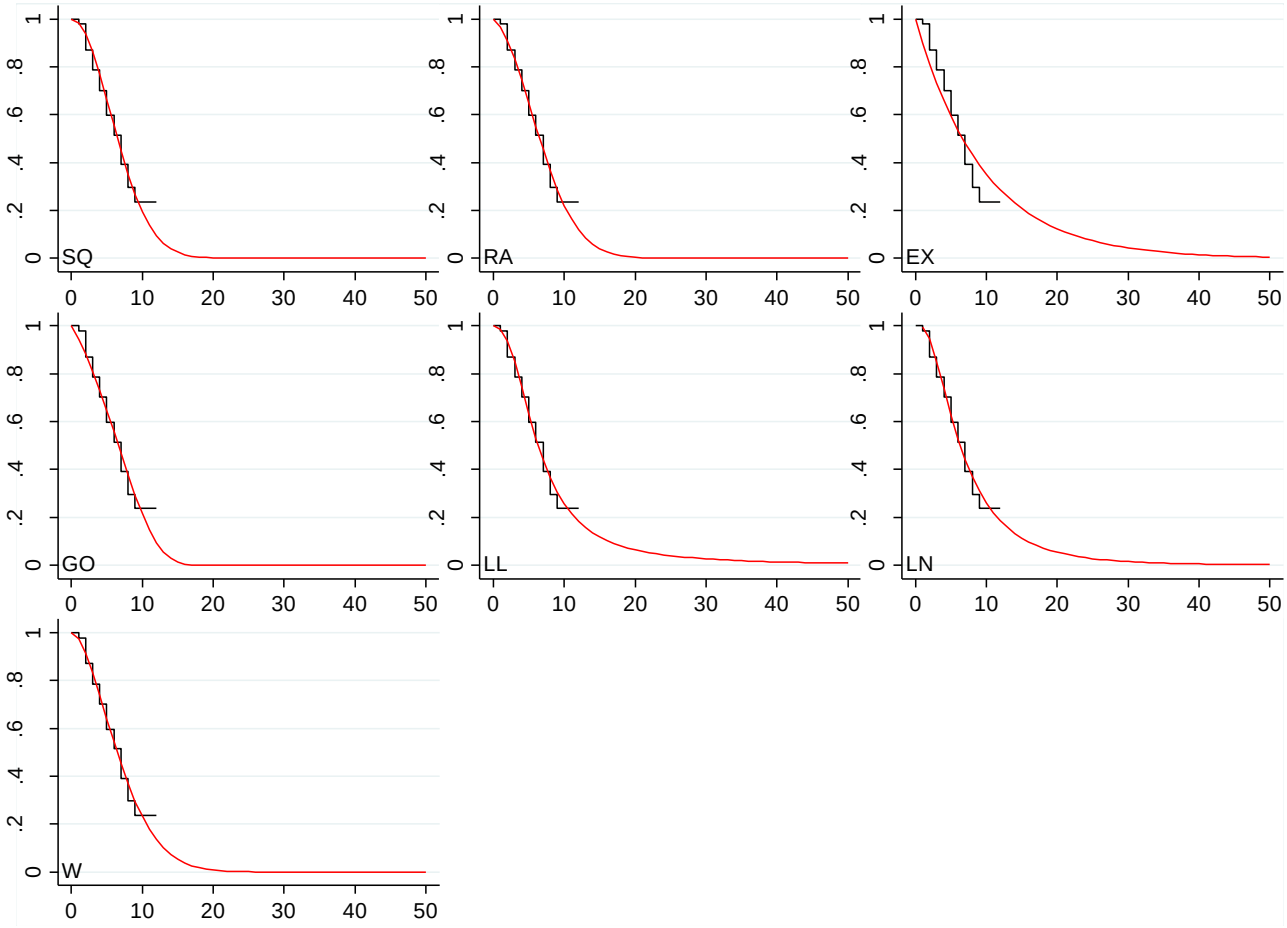
Analysis time = years. Vertical axis = proportion not failed.

Figure 50 Nawaz et al. 2014 model fits ACI grade 0 degradative change



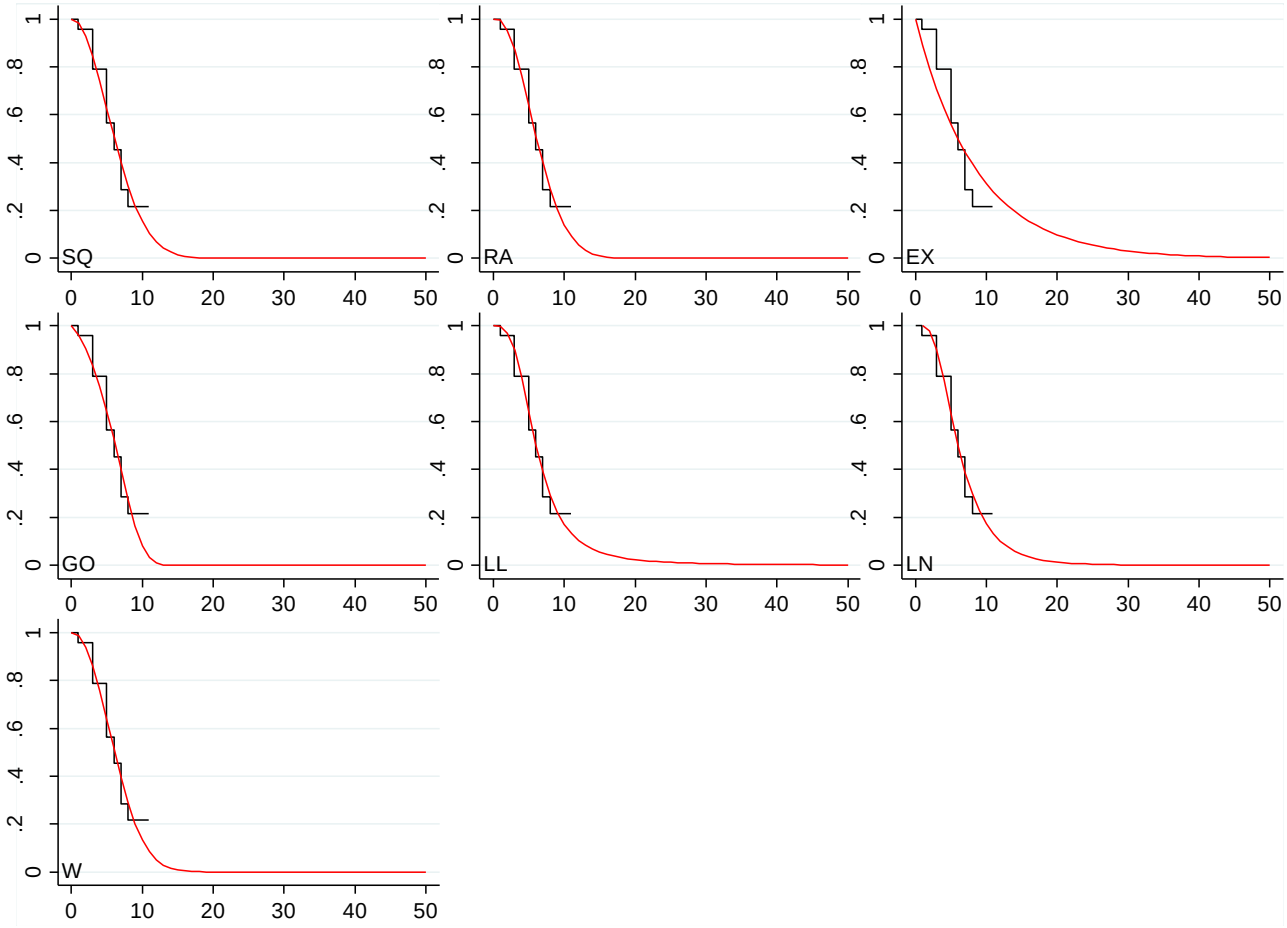
Analysis time = years. Vertical axis = proportion not failed.

Figure 51 Nawaz et al. 2014 model fits ACI grade 1 degradative change



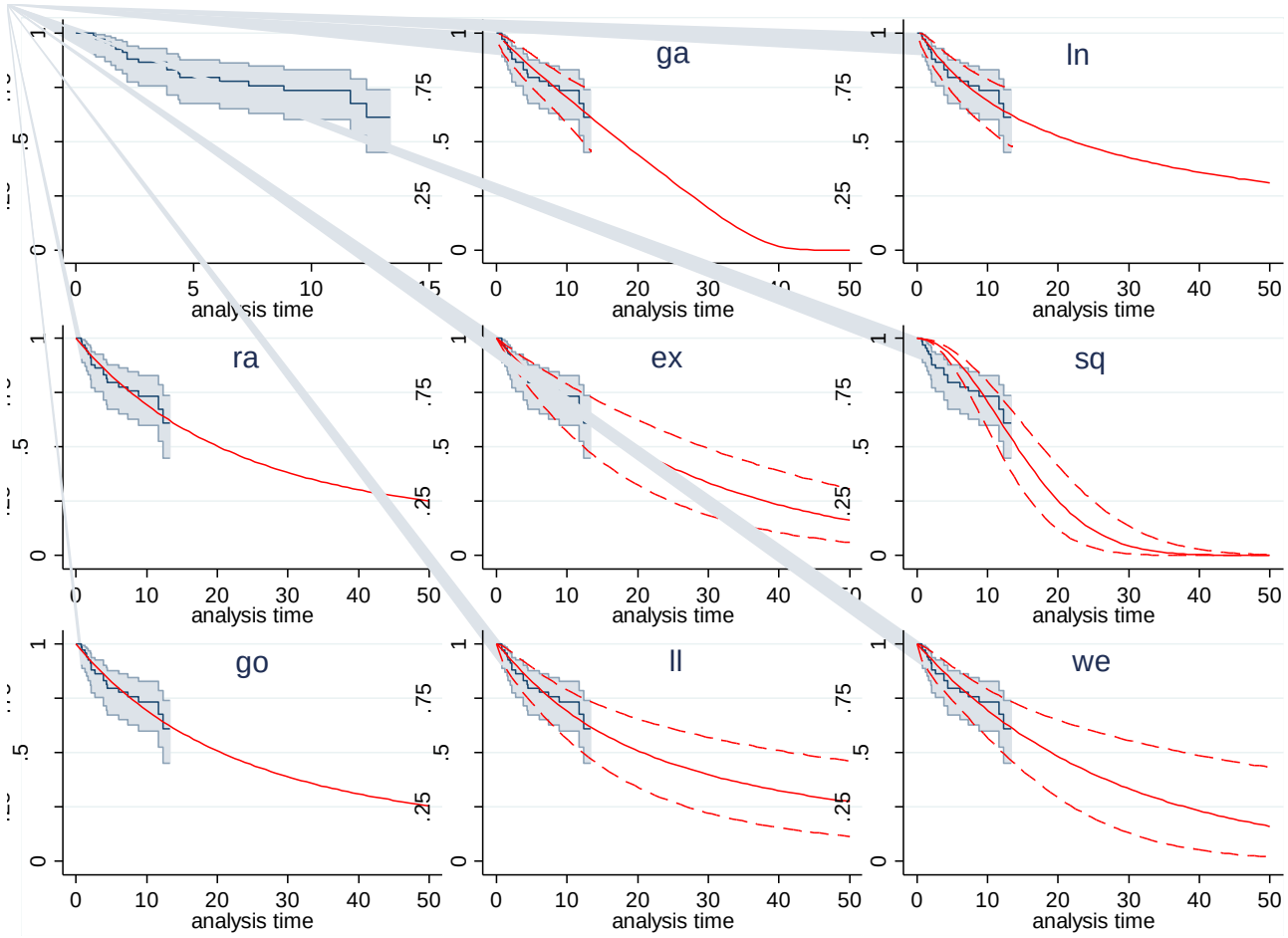
Analysis time = years. Vertical axis = proportion not failed.

Figure 52 Nawaz et al., 2014 model fits ACI grade 2 degradative change



Analysis time = years. Vertical axis = proportion not failed.

Figure 53 Nawaz et al., 2014 model fits ACI grade 3 degradative change



Analysis time = years. Vertical axis = proportion not failed.

Figure 54 Niemeyer 2014 model fits ACI

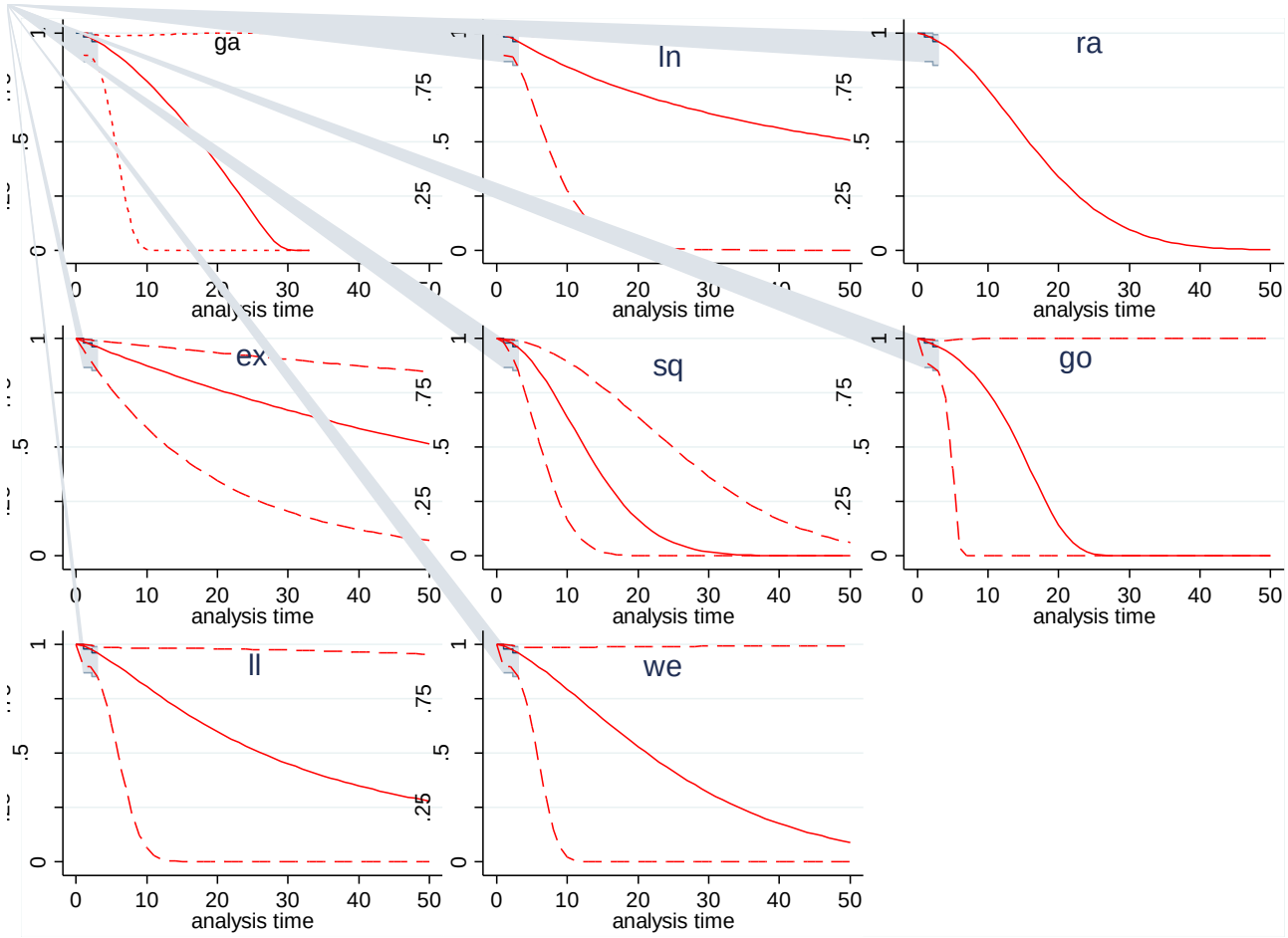


Figure 55 Saris et al., 2009 ACI arm

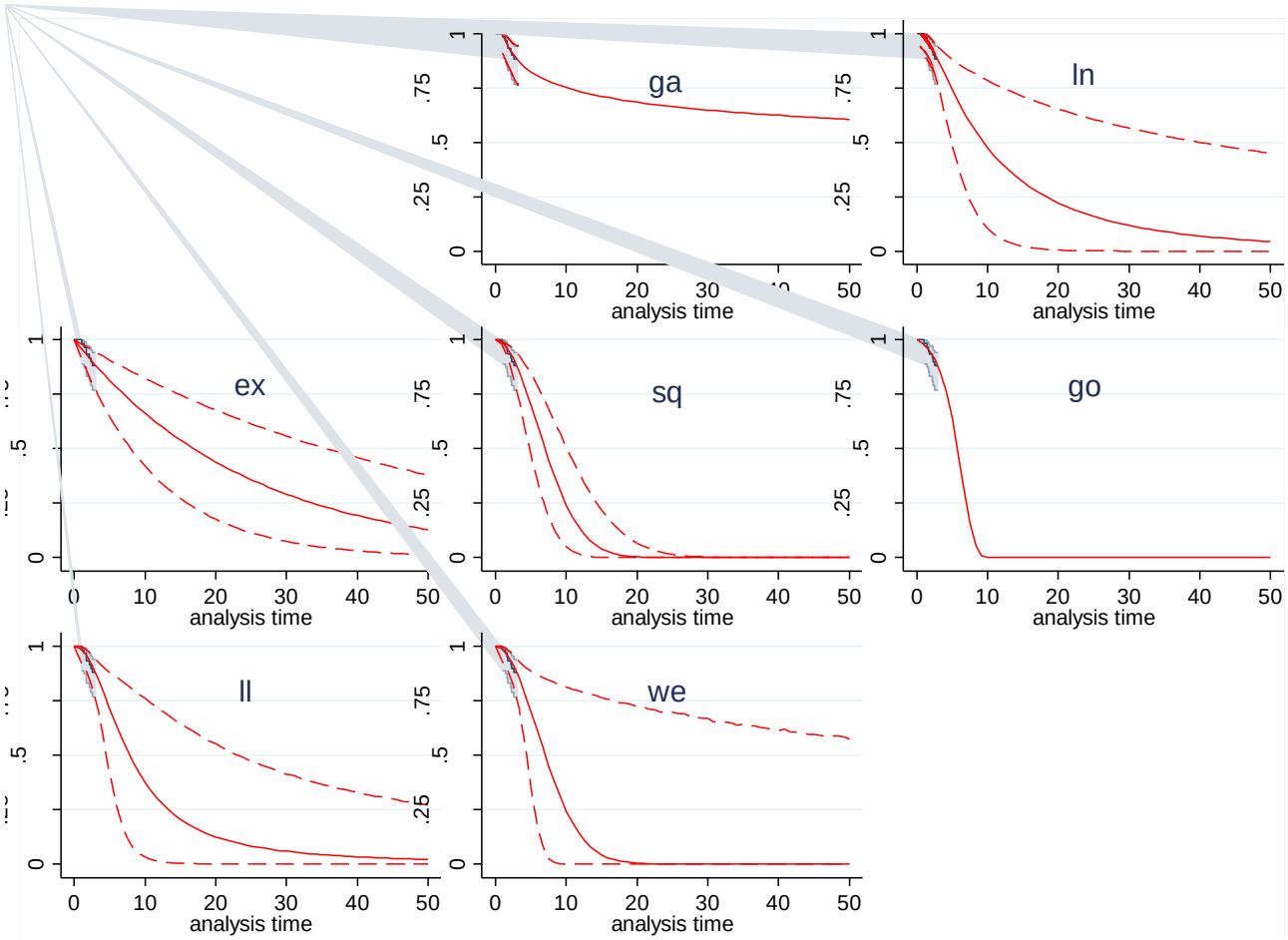


Figure 56 Saris et al., 2009 MF arm

.

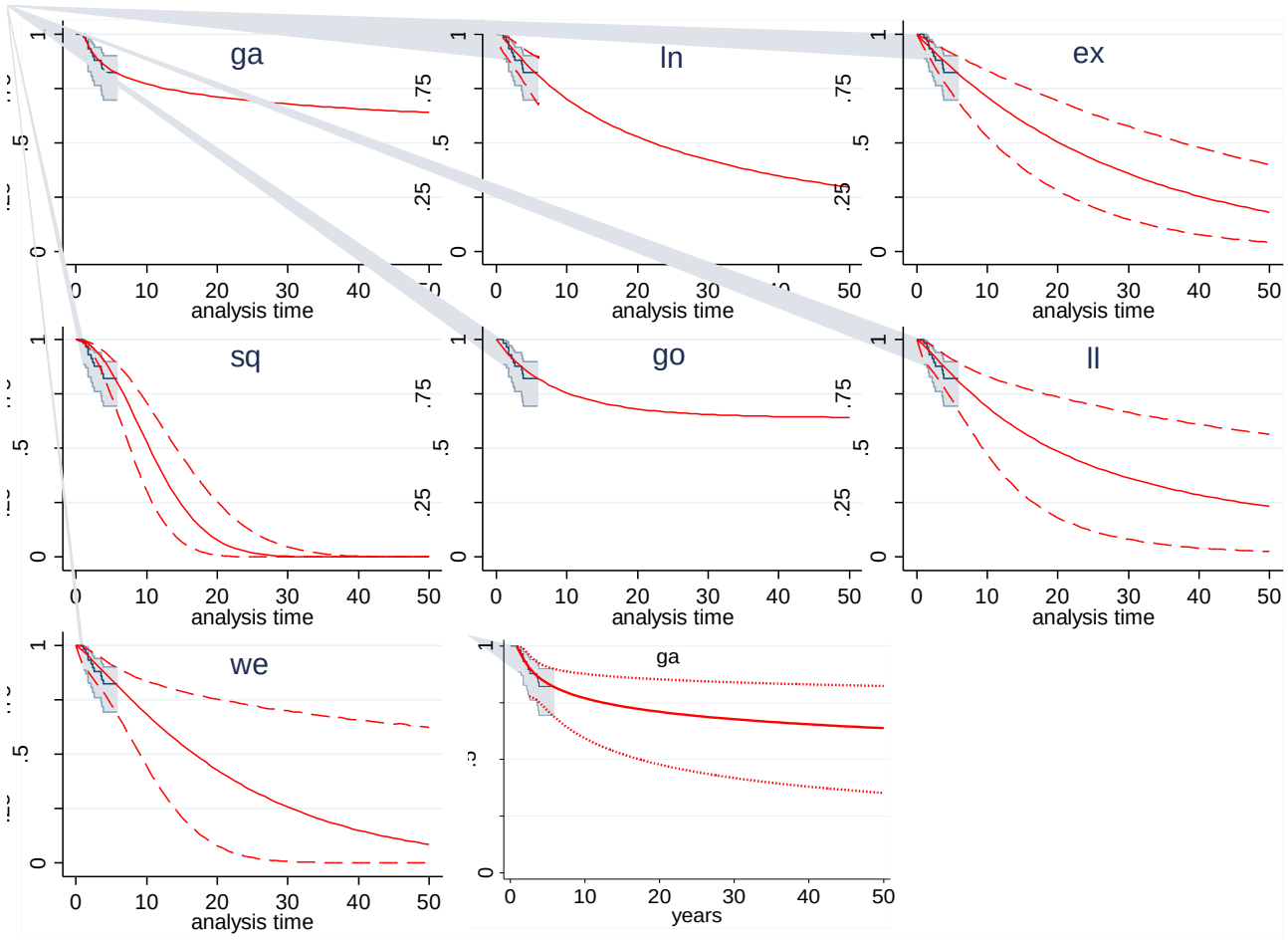


Figure 57 Vanlauwe et al. 2011 MF arm model fits; IPD reconstructed without risktable data

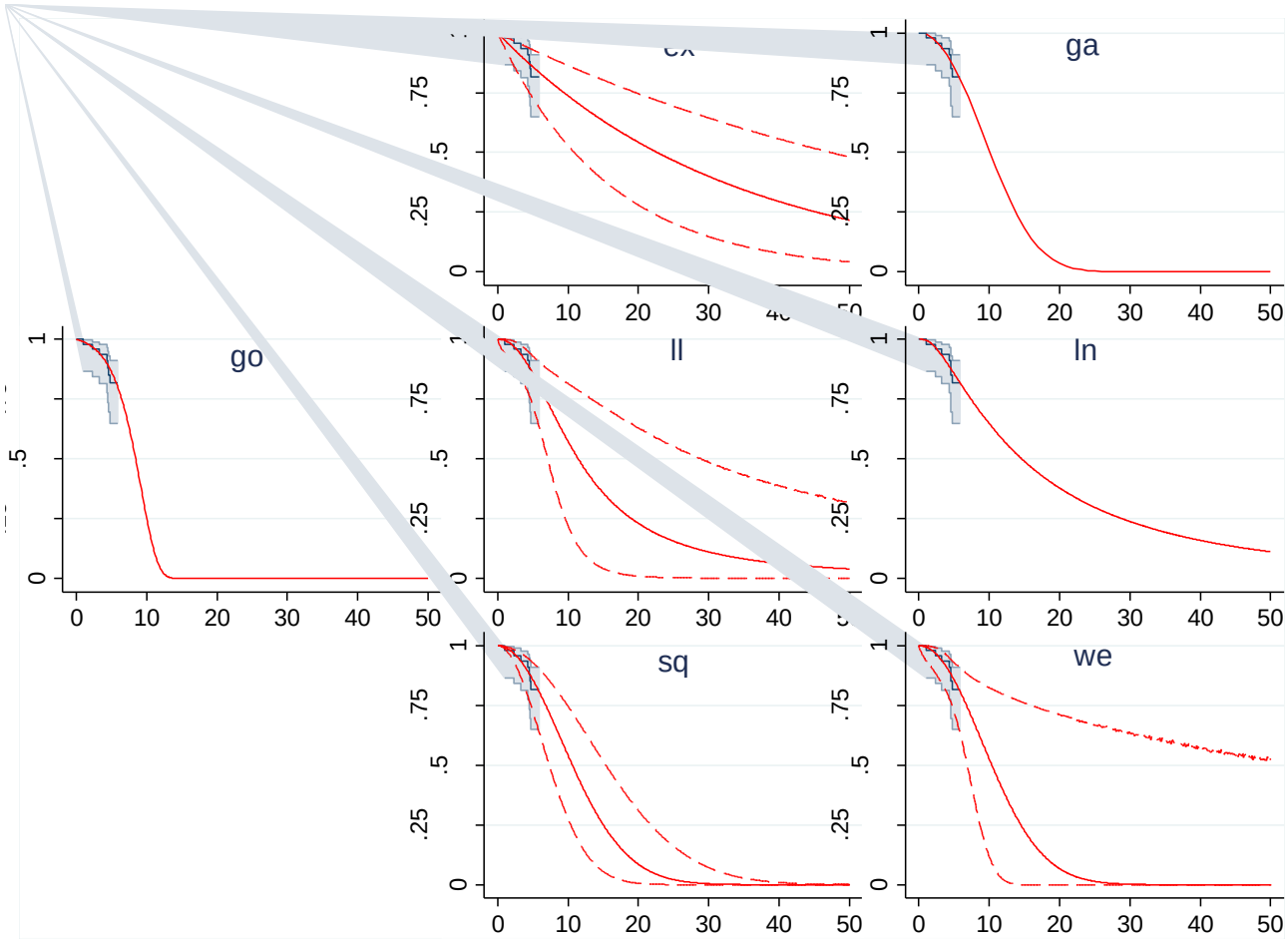


Figure 58 Vanlauwe et al., 2011 ACI arm model fits

Appendix 6 Failure of ACI after previous MF (Minas 2014)

Failure after MF. Note: only 13 patients were analysed. Data extracted from published grapH and graph redrawn.

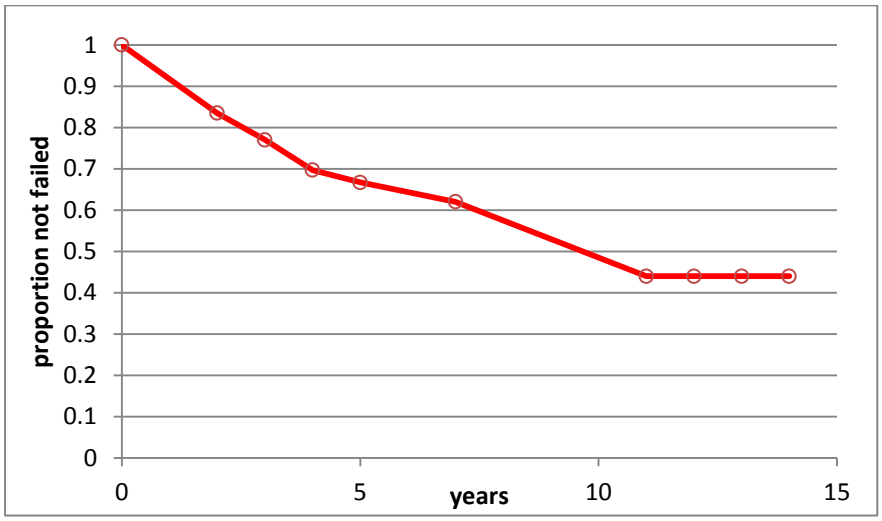


Figure 59 Failure after previous MF – Minas 2014.

Appendix 7 Potential anomalies in the Vanlauwe et al., 2011 published report

The KM plot for MF has 10 steps and a total of 10 events were reported (one step for each event). Seven steps occur before 36 months, two of these very close together at about 20 months (red arrow), and 3 steps occur after 36 months. This does not tally with the data in Appendix 1 which depicts five MF re-interventions occurring before 36 months and five after 36 months. For the ACI KM plot two steps occur before 36 months and five after 36 months and this corresponds to the data provided in Vanlauwe Appendix 1. The risk table for the MF arm is anomalous in that the number at risk is reported as increasing at 36 months. It is unclear what the correct numbers should be at 24, 36 and 48 months for the MF risk table. Taken together the inconsistencies between KM plot and Appendix and the anomalous risk table data mean that MF results for time to failure in Vanlauwe are unlikely to be reliable.

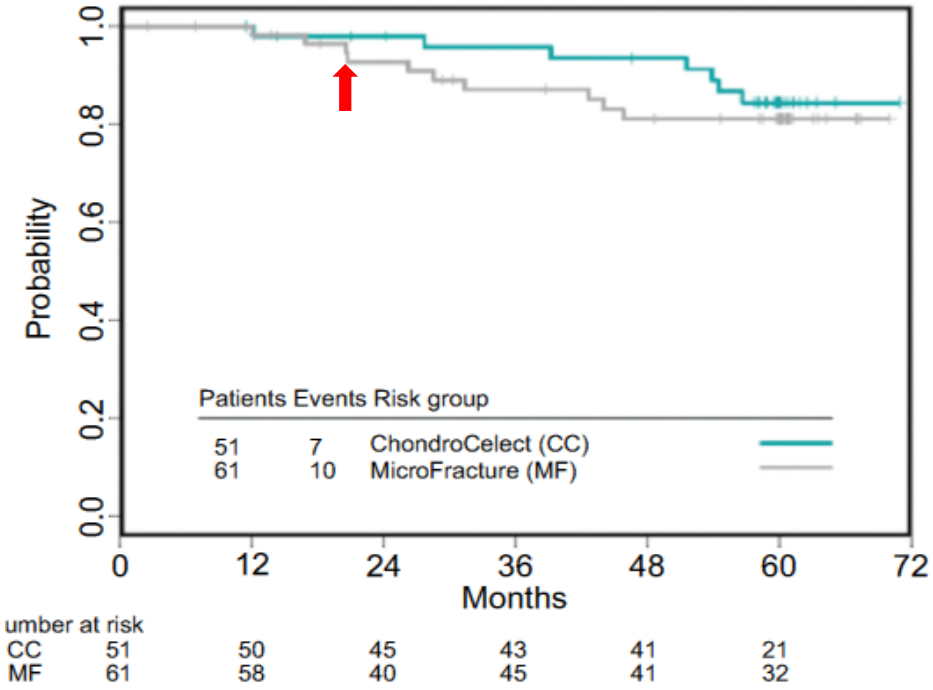


Figure 60 Time to failure – Vanlauwe 2011

The AG requested clarification regarding the risk table and received to following reply:

Once again sorry for the time we took for answering your questions.
Regarding your question about the number of patients analysed in the survival curve:
The lower numbers at 24 month and 60 month are due to the fact that in the Figure 3 (KM curves), we use the exact time (calculated from the dates) to treatment failure. So in this graph a lot of patients were censored a few days before M60 because they did the visit a few days before the theoretical visit

at M60. Consequently, they are not counted in the risk set at M60 since they are censored at 59.xxx months. The same holds true for other time points.

Personally I think that this is a strange way of handling of patient numbers (but I'm not a statistician). So for example patients that did attend the 24 month visit early, or skipped this visit, were not counted in Figure 3 for the 24 month visit even though they had a later visit at which the implant was still intact.

If the 40 MF patients at risk at 24 months is changed to 50 (intermediate between 58 at 12 months and 45 at 36 months) under the assumption of a copy editing error in the risk table then the Guyot et al. method reconstructs a Kaplan Meier plot (Figure below) that is superimposable on the published plot.

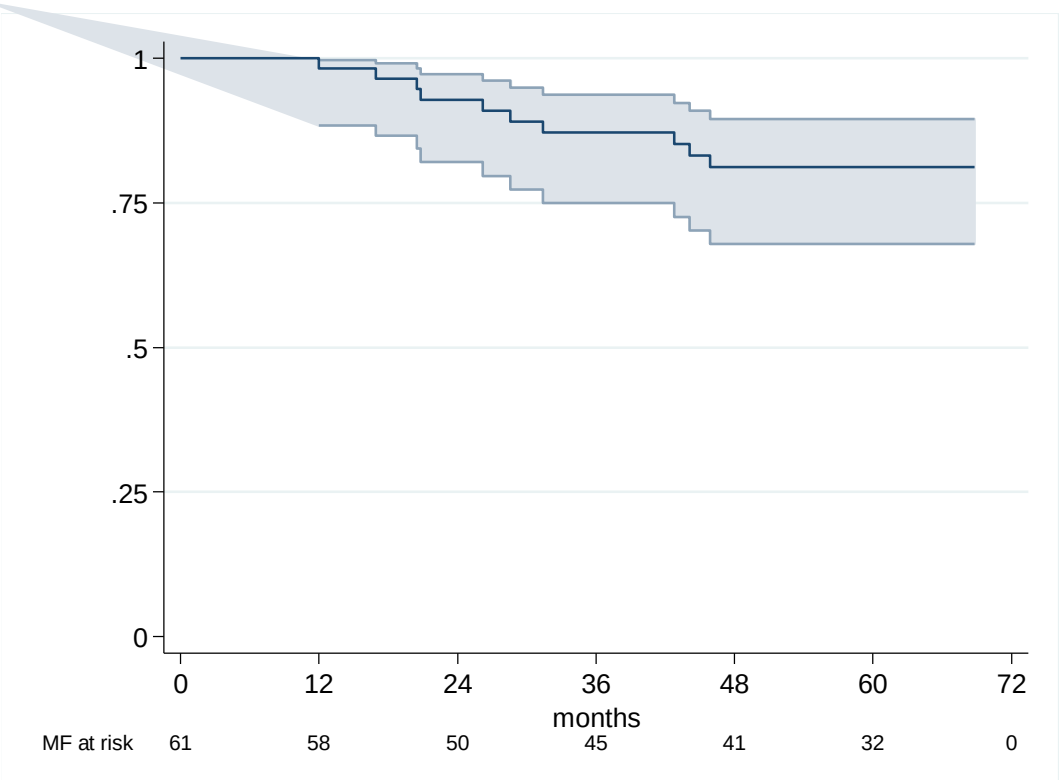


Figure 61 KM plot constructed from Vanlauwe data

According to information criteria exponential and gamma distributions provided the best parametric fit to this IPD (Table below). The gamma model predicted that more than half patients remained without failure for 70 years.

Table 28 Model fits for reconstructed Vanlauwe KM plot

Model	Obs	ll(model)	df	AIC	BIC
gamma	61	-31.5741	3	69.14825	75.48087
exponential	61	-34.7675	1	71.53493	73.6458
weibull	61	-34.5122	2	73.02446	77.24621
gompertz	61	-34.7407	2	73.48149	77.70324
lognormal	61	-33.6505	2	71.301	75.52275
loglogistic	61	-34.3055	2	72.611	76.83275
Linearly increasing hazard (1 parameter)	61	-36.0882	1	74.17634	76.28721

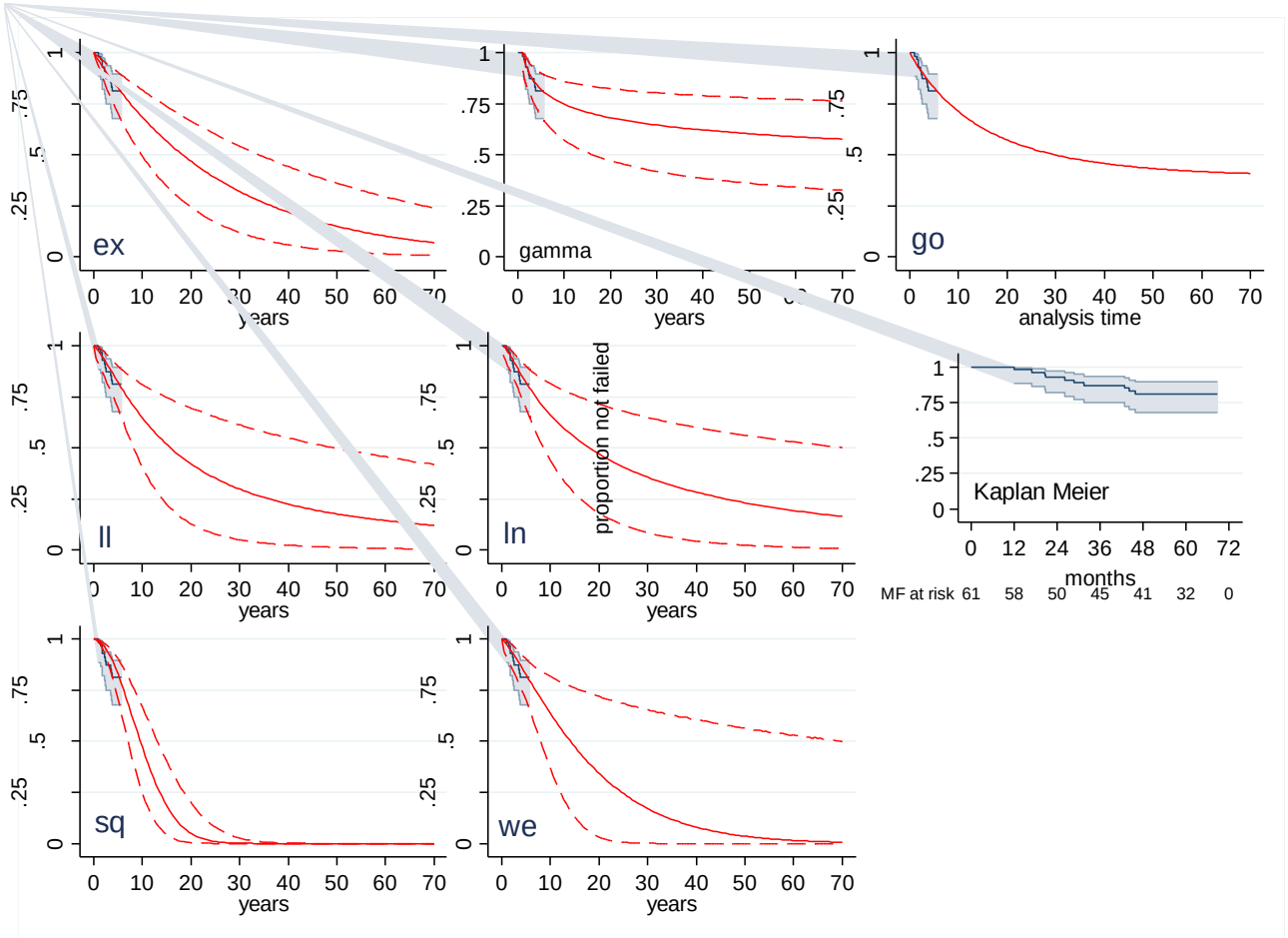


Figure 62 Summarises the parametric fits when using this reconstructed IPD

Ordinate = proportion not failed.

Appendix 8 Gudas et.al 2012 RCT

In the microfracture arm of the Gudas et al., 2012 [36]study there were 11 failures in 10 years follow up. Participants were athletes including many professionals. Failure was defined as need of a reoperation because of symptoms due to primary defects. All 11 failures occurred in first 3 years then none to 10 years giving an extended flat tail to the KM plot. No risk table was presented. Table 29 summarises the information criteria for parametric fits to reconstructed IPD derived from the published KM plot.

Table 29 Information criteria for parametric fits, Gudas study.

Model	Obs	ll(model)	df	AIC	BIC
exponential	29	-29.0939	1	60.18781	61.55511
weibull	29	-28.9866	2	61.97326	64.70786
gompertz	29	-28.6264	2	61.25283	63.98742
lognormal	29	-26.7302	2	57.46045	60.19504
loglogistic	29	-27.3641	2	58.72812	61.46271
linear hazard (1 parameter)	29	-34.2149	1	70.42974	71.79703
linear hazard (2 parameters)	29	-29.0939	2	62.18781	64.9224

A lognormal model provided the best fit according to information criteria. Figure 63 summarises the lognormal model and other parametric fits extrapolated to 50 years.

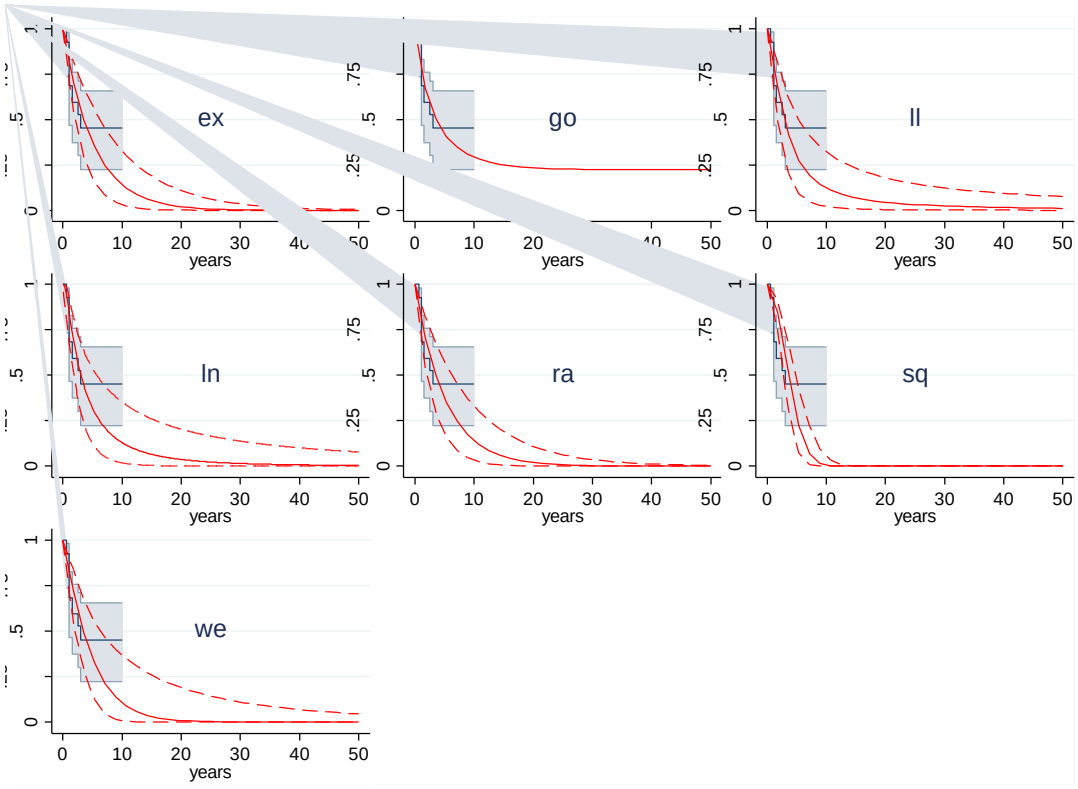


Figure 63 Gudas data parametic fits

The lognormal model predicts worse performance for MF than best fit models using data from Saris, Knutsen and Layton; these are compared in the Figure 64 below.

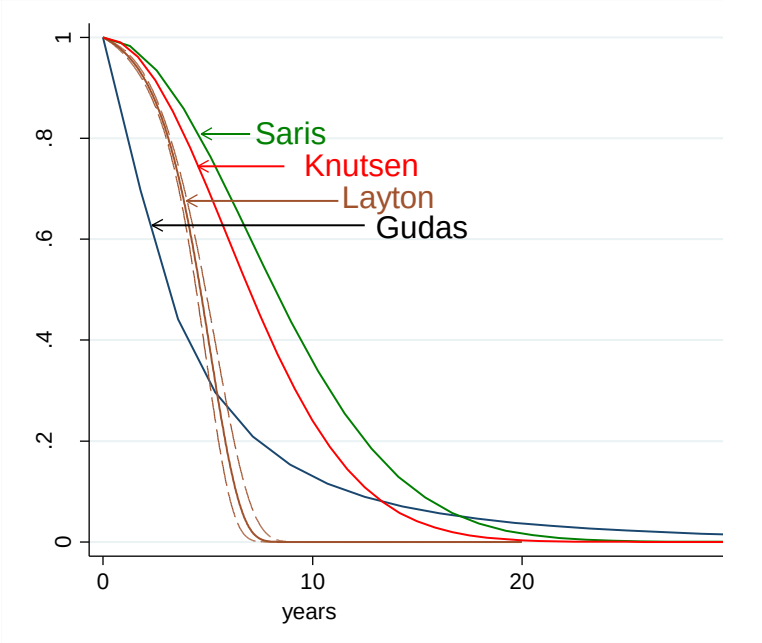


Figure 64 Lognormal fits Saris, Knutsen and Layton data

Appendix 9 ACTIVE trial first submission, time to treatment failure

Figure 65 shows the submission Kaplan Meier plot for time to treatment failure.

Figure 65 KM plot for failure, ACTIVE data

Figure 66 shows the Kaplan Meier plot from reconstructed IPD for the ACI arm together with the best fitting parametric model (bath tub) for ACI treatment failure that predict all have failed by 15 years (180 months).

Figure 66 ACTIVE trial Kaplan Meier plot from reconstructed IPD

Information criteria values for all the tested models are summarised in Table 30.

Table 30 Information criteria for parametric models of treatment failure (ACI arm Oswestry)

Model	Obs	ll(model)	df	AIC	BIC
gamma	195	-260.3752	3	526.7504	536.5694
exponential	195	-285.5689	1	573.1377	576.4107
weibull	195	-272.9812	2	549.9625	556.5085
gompertz	195	-281.1102	2	566.2203	572.7663
lognormal	195	-297.6517	2	599.3034	605.8494
loglogistic	195	-283.4075	2	570.8151	577.3611
bathtub	195	-224.4628	3	454.9255	464.7445
Linearly increasing hazard (1 parameter)	195	-285.5689	1	573.1377	576.4107
Linearly increasing hazard (2 parameters)	195	-282.7383	2	569.4765	576.0225

Model fits are summarised in Figure 67.

Figure 67 Model fits ACTIVE data, ACI arm

Figure 68 summarises parametric models fit to reconstructed IPD for the standard treatment arm of ACIVE.

Figure 68 Parametric models fit to reconstructed IPD for the standard treatment arm of ACIVE.

According to information criteria a gamma distribution provided the best parametric model fits for reconstructed IPD for the standard treatment arm (Oswestry submission). This shown in Figure 69 compared with models for microfracture arms of other studies.

Figure 69 Gamma distribution standard treatment ACTIVE study compared to other MF studies.

Response to additional assessment group report on Autologous Chondrocyte Implantation.

25th February 2017.

On behalf of The British Association for Surgery of the Knee

1. UK Knee surgeons are pleased that NICE have finally put this important subject back on their agenda. There has been clinician dismay at real patient suffering and denial by the NHS and healthcare funders of appropriate treatment due to the delay of 2 years in re-evaluating the initial erroneous NICE provisional recommendation. The delay has also been very detrimental to investment in regenerative medicine research in the UK.
2. The provisional recommendation by NICE was discussed at the BASK Annual Congress. There was consensus that it was poor decision making, at odds with the published evidence, and likely arisen due to one vociferous but under-informed surgeon at the Appraisal Meeting that raised the idea to the committee that there was not consensus amongst knee surgeons where in fact there is. There was overwhelming support for ACI from the BASK Congress based on the evidence available.
3. The Consensus Meeting of UK Cartilage Surgeons in 2014 examined all the evidence and produced a consensus paper published in 2015. This supports ACI as primary treatment for articular cartilage defects in all but the smallest area of damage. Further evidence has now arisen that even small defects may be best served with ACI to gain best pain relief and most durable result. The UK Consensus paper was signed by 104 colleagues, and is in line with similar consensus papers from the Netherlands and Germany.
4. ACI is not new technology. We have a 30th Anniversary Celebratory Congress of the first ACI this year. There are multiple cohort and RCT studies over 10 years. We have better evidence to support the efficacy of ACI than almost any other orthopaedic intervention. Delays by NICE to acknowledge established efficacy of ACI is stalling progress in evolution of newer treatments in the UK.
5. The key messages from BASK, supported by the additional assessment group report are:
    a. The quality of the SUMMIT and TigACT surgical trials are good. Surgical trials are much harder to conduct that drug trials and this must be acknowledged. They cannot be compared to drug trials.

b. The evidence of the assessment group supports the efficacy and health costs of ACI
c. Cost of ACI per QALY or assessment of ICER compared to other interventions, already readily approved by NICE, is low. It is potentially restorative to normal function, not palliative.
d. ACI is performed in working age patients; the report does not evaluate the wider financial viability and cost benefit to society of this intervention.
e. ACI is the ONLY treatment with efficacy in the larger articular cartilage defects. Patients are otherwise left in pain.
f. ACI works best when performed as first-line treatment. Although it is the only viable option for salvage of previously operated defects, the effectiveness is best when done as the primary surgery. This is in line with the GIRFT principles of getting it right first time; correct indication, correct patient, correct surgery
g. UK Knee surgeons acknowledge the necessity of ongoing collection of efficacy and health economic data of ACI along with all other surgery. There is no objection to mandating ACI into a Registry in line with joint replacement surgery. A suitable Cartilage Registry operated to UK standard is available free of charge to all participants and provided by the International Cartilage Repair Society. The ICRS Registry data management partner (Amplitude) is UK based and runs several UK orthopaedic registries.

Comments from the Robert Jones & Agnes Hunt Orthopaedic & District Hospital NHS Trust (RJAH) Oswestry on "Autologous chondrocyte implantation in the knee: additional analyses" by Warwick evidence, published on 1 March 2016

We thank NICE for providing us with the opportunity to comment on the report on the additional analyses performed by the assessment group (Warwick Evidence). We are in support of the contents, but have some specific comments that we think provide further backing to the models in the report. In addition, we have some additional comments that we think are relevant to the matters analysed in the report.

Specific comments

1. We fully support the conclusion in the report by Warwick Evidence that NICE might consider ACI cost-effective based on the Incremental Cost Effectiveness Ratios (ICERs; page 17) calculated in the report.

2. We now have further evidence to support the modelling of long-term failure by Warwick Evidence of ACI and microfracture as secondary repair procedures (Chapter 2).
In October 2015 we supplied NICE in confidence with the patient-level EQ-5D data from the ACTIVE randomised controlled trial of ACI versus alternatives as a second cartilage repair procedure after a failed earlier procedure. At the time, a full dataset of 5-year outcomes including survival was not yet available, but this data has now been collected and analysed by statisticians from the Birmingham Clinical Trials Unit. One primary outcome of the trial was "cessation of benefit", with a definition similar to but more exacting than the definition of "failure" used in the Nawaz study that informed much of the modelling by Warwick Evidence. The Nawaz study used data from a Centre of Excellence and found a survival rate of 59% at five years for ACI in patients with a failed previous treatment. Patients in ACTIVE were enrolled from 27 hospitals in the UK and two from Norway, and found a survival rate of 51% at five year for ACI in the same group of patients. We believe that this supports the use of the data from the Nawaz study to model long-term failure of ACI in patients who had previous treatment. The survival rate for alternative treatments in patients in ACTIVE was 50% at five years, which would support the use of the Layton data in the report by Warwick Evidence as comparator group in the long-term survival analyses.

3. We now have evidence to refine the conclusion "ACI will give better results if used as first repair procedure" (page 17).
The conclusion that ACI will give better results if used as a first repair procedure leans heavily on the Nawaz study. The Nawaz study considers previous microfracture, drilling and mosaicplasty as "previous procedures" but does not consider previous debridement as a previous procedure. We now have data from the ACTIVE randomised controlled trial that supports neglecting previous debridement as a first repair procedure.

A planned subgroup analysis was performed to determine the effect of previous treatment types (marrow stimulation, i.e. microfracture or drilling, versus other procedures) on treatment outcome. The analysis of ACTIVE data found a significant interaction effect between treatment (ACI or alternatives) and nature of the failed first repair procedure. The

mean benefit of ACI over alternatives in patients who did not have previous marrow stimulation was 9.3 points higher than that in patients who did have previous marrow stimulation (p=0.03). This was measured using the Lysholm knee scale and corresponds to an effect size of 0.4 times the standard deviation. We believe this data supports the view in the Nawaz study that procedures such as debridement or washout should not be counted as previous repair procedure when considering the utility of ACI. The key conclusion on page 17 might therefore be refined to **"ACI will give better results if used as first repair procedure or as secondary repair procedure after debridement or washout".** See also comment 6 below.

4. Academic departments in collaboration with NHS cell production facilities using MHRA governed and licenced units can provide cells at low costs (page 15)
The RJAH can provide a complete ACI treatment episode for a cost of £9,159 to £12,361, depending on the exact nature of the cartilage defect. This price includes all overheads where the cells are both harvested, manufactured in our cell facility and provided within our Trust. The report demonstrates that the costs of cells are the prime determinant of the ICER, and our Trust can provide the complete procedure within the lowest total costs of £9266 assumed in the report (section 3.2.2, page 54). We therefore believe the foreseeable future for cell therapies in the UK is provision by with low overheads and no commercial costs.

Additional comments

5. Numbers of Patients
a) Providing a tertiary referral service from Oswestry over the last 20 years, we have treated an average of 30 patients annually until this last year.

b) The number of patients in the UK eligible for treatment by ACI is relatively small, as we already alluded to in our original submission to NICE of September 2014. If NICE were to support the use of ACI in primary defects only then we assess 300 patients a year would be treated in the UK. With adequate reimbursement costs, other centres (who we would happily assist to get established) would be encouraged to grow cells.

6. The Oswestry Risk of Knee Arthroplasty Index (ORKA)
Oswestry has now published a tool (Oswestry Risk of Knee Arthroplasty Index or ORKA) that predicts the survival of ACI until knee arthroplasty, based on several baseline variables besides previous surgery. If this tool is used during patient selection we estimate that the survival of patients at ten years without proceeding to total knee replacement would reach 90%. We propose to externally validate and adopt this tool during patient selection.

7. We propose that ankle ACI is considered equivalent to knee ACI. It is a similar joint and we and other centres have reported very encouraging results. In rheumatoid arthritis a case is not made for each separate joint when a therapy is considered by NICE. There will only ever be very small numbers of patients and no basis for a clinical trial that can deliver useful results. The total demand in the UK will be less than 50 to 100 cases per year.

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Dear Jeremy

Vericel acknowledges the receipt and review of the Warwick Assessment Report. We are very pleased with the level of detail and understanding of the disease state. The Warwick Group conducted a thorough systematic search of the literature and identified 6 relevant publications of long-term data to incorporate into the analysis to assess the clinical and economic benefit of autologous chondrocyte implantation. The Nawaz 2016 study was the main focus of the analysis. This appropriately reflected the UK experience with Autologous Chondrocyte Implantation (ACI.

The Nawaz 2016 study was conducted at the leading Cartilage Repair Center in the United Kingdom – the Stanmore Orthopaedic Hospital. The study included 827 patients with mean defect size 4.09 cm^2 and 6.2 years of follow-up. The study demonstrated ACI graft survival of 78% at 5 years and 51% at 10 years for the full cohort. Outcomes were much poorer in patients who had a previous surgical intervention violating the underlying subchondral bone, with a failure rate 4.72 times higher than those without previous intervention.

The presence of osteoarthritis (OA) also increased the ACI failure rates, especially in patients with Kellgren-Lawrence grades 2 and 3. Only 25% of these patients had graft survival to 10 years. By using the full cohort (including patients with prior interventions and early degenerative joint disease) for inclusion in the cost-effectiveness model, this study represents a very conservative estimate of effectiveness of ACI, but provides insight into the true UK experience.

The cost-effectiveness (CE) was based on information extrapolated from the Nawaz 2016 study (full cohort used in the cost-effectiveness model). At ~30 years, approximately 90% of patients fail ACI. For patients without previous interventions, 70% fail after 70 years, 60% after 50 years and all MF patients fail after ~20 years based on Kaplan-Meier (KM) plots for time to failure. To

determine microfracture failure rates, pooled data were used from the long-term studies. (Layton, 2015 Value in Health, Knutsen, JBJS 2007, Saris AJSM 2009).

The costs used in the cost analysis included:

- Cost of harvesting of the biopsy: £870
- Cost of implantation: £2,396, and
- Cost of the cultured cells £16,000.

Results of the assessment report showed the cost analysis to have an incremental cost-effectiveness ratio (ICER) of £19,000, and when applying the utility data provided by Vericel, it reduces the ICER to £15,700.

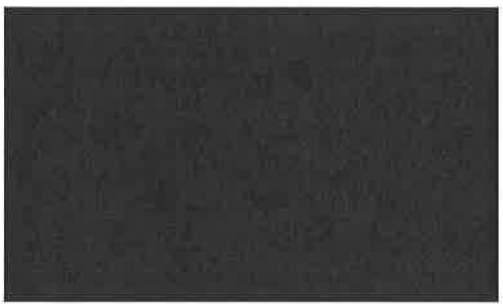
The clinical and economic evidence supports the use of ACI with a favorable cost benefit ratio. The best use of ACI is a first-line rather than a second-line treatment option. The best treatment algorithms use ACI or MF in first-line depending upon the size of the lesion, and only ACI as a second-line treatment option. Microfracture was demonstrated to be inferior as a treatment when used second-line regardless of first-line treatment. ICERs in early Degenerative Joint Disease also appeared acceptable. From the conclusion of the Warwick assessment, ACI will provide better results if used as the first repair procedure and provides an advantage over microfracture in the long-term.

Vericel is pleased with the comprehensive approach of the Warwick Assessment. We hope that the economic analyses produced ICERs are considered acceptable by NICE. Vericel would like to acknowledge the time and effort that went into this thorough assessment and allowing us the opportunity to review.

Vericel would like to request a confirmation of the date that the NICE committee will meet to make a decision, and the date the decision will be rendered and published.

Thank you very much.

Sincerely,



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We appreciate the work that the Warwick Medical School invested in this updated analysis.

There are four points we would like to comment on:

1. Level of evidence for ACI vs. Microfracture (MFX)
2. The failure rate of ACI
3. Size of lesion and impact on outcomes
4. Five year outcomes with MACI that showed sustained durability

Vericel agrees that the evidence for ACI was more substantial than that found for MFX. In a recent meta-analysis published by Riboh in 2016, ACI had more Level I & II studies compared to MFX. Also, ACI was the highest ranked treatment when outcomes where considered.

We also noted that failure rate was an important focus of the analysis. We agree that a high percentage of patients treated in the studies assessed were chronic patients that had failed multiple interventions. Globally, ACI has often reserved to treat more challenging lesions such as early OA, degenerative lesions, and large chronic lesions that have failed multiple treatments.

Cartilage defects of the knee occur along a spectrum of disease and severity. Larger, more chronic lesions are symptomatic lesions and can cause disabling symptoms such as pain, catching, locking, and swelling. If these larger chondral lesions are left untreated, it may progress to debilitating joint pain, dysfunction and degenerative arthritis. The key question is: what treatment option can you offer them?

This treated population matches the real world situation of patients who can benefit from ACI. The Brigham and Women's 20 year data base of over 800 patients (Brigham and Women's Hospital, Cartilage Repair Center Registry, Boston MA USA) the vast majority of patients have more than one defect. Lesions include all surfaces of the knee which respond well to ACI. There are few treatments that are able to treat these larger lesions or lesions found in the patellofemoral joint other than ACI reproducibly well with greater than 80% patient satisfaction and good - excellent results for which MFX fares poorly [7] Most cartilage repair surgeons would

also agree that ACI is a valid treatment option for cartilage in the patellofemoral articulation, and for large multiple lesions in the knee joint. This was noted in the significant response physicians provided to the committee over a year ago where they emphasized the importance of being to offer a treatment to younger patients who either did not want or were too young for a TKA.

We also acknowledge that Microfracture, (MFX), "Does Burn Bridges" when it comes to the treatment of failed MFX treatments with ACI, as the failure rate is 3-6 times worse than a primary ACI without prior violation of the subchondral bone.[3,10,11,12] ACI was considered a second-line therapy, because it lacked a Phase III superiority clinical study. Both the FDA and EMA approved MACI as a first-line treatment option

A key consideration in choosing the appropriate cartilage regeneration technique is the size of the cartilage lesion. The prognosis is worse when the defect is greater than 2 cm^2 in the weight-bearing portion of the articular surface.

Knutsen et al. [2007] found no difference in outcomes with MFX in lesions less than 4cm^2, however, ACI did better in larger lesions. In contrast, Bentley et al. [2012], concentrating on large lesions isolated to the medial femoral condyle, determined that the early results (19 months) were superior with ACI (mean area 4.8 cm^2) compared to OAT (mean area 5 cm^2). Vanlauwe et al. determined that there was no difference in KOOS outcome measures comparing CCI and MFX at five-year follow-up in the treatment of lesions with a mean area of 2.6 cm^2 and 2.4 cm^2.

In the SUMMIT Trial, for a subgroup analysis of the group with larger lesions (> 4 cm^2), MACI was superior to MFX (KOOS response rates 97% vs. 77%). In the group with smaller lesions (< 4 cm^2), where MFX is considered the treatment of choice, there was also a benefit for MACI (KOOS response rates (78% vs. 61%). Overall, the benefit of MACI is not restricted to a particular size of lesion and is a viable treatment option for lesions >3cm^2 in active individuals.

When focusing on five year durability with focal chondral lesions

There have been three studies published from Australia, Germany and Austria with a minimum of five year follow-up. The outcomes were consistent with the findings of the SUMMIT trial. Clinical improvements in function and pain relief were seen as early as 36 weeks and maintained for five years. A four year study from the United Kingdom also showed similar

outcomes greater than five years in osteochondral lesions. Ebert, 2011, Basad, XX Marlovitis, 2012 and V.

New information KOOS Subscale Results for the Five Year Extension Data

For patients who chose to participate in the Extension study, the improvements in KOOS pain and function scores were maintained over an additional 3 years of follow-up (5 years total). Change from baseline in KOOS pain and function over time is shown in Figure 1. As shown in the figure, the improvements in MACI and MFX extended consistently with separation of the 2 curves maintained over time.

Mean actual scores in all KOOS subscales at Year 2 (SUMMIT) and Years 3 and 5 (Extension study) are shown in Table 1. Across all subscales, actual mean scores were notably consistent over time. It should be noted that the responder analysis was likely affected by missing data, especially at Year 3 where six enrolled MFX patients (0 enrolled MACI) did not have data. The results that occurred at year 2 were maintained at five years.

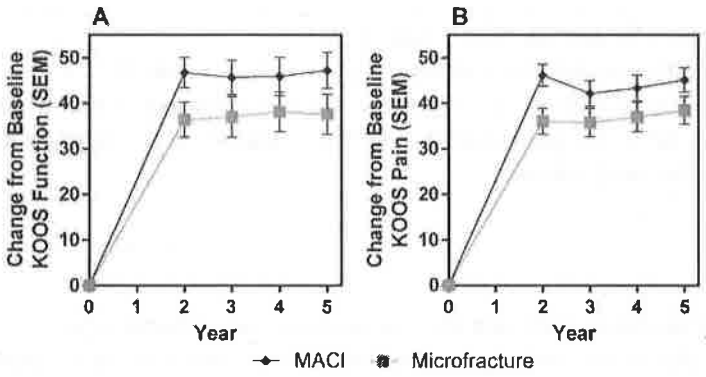

Figure 1: Change from Baseline in MACI and Microfracture KOOS Pain and KOOS Function Scores over Time (Observed Data)

Table 1. Mean Actual Scores at Year 2 in SUMMIT and Year 5 in SUMMIT Extension

	MACI					Microfracture				
KOOS Subscale	**n**	**Year 2**	**n**	**Year 3**	**Year 5**	**n**	**Year 2**	**n[a]**	**Year 3**	**Year 5**
Pain	72	82.5 ±	65	79.2±2	82.2 ±	70	70.9 ±	57/59	72.3±22.3	74.8 ± 21.7

		16.2		0.1	20.1		24.2			
Function	72	60.9 ± 27.8	65	60.9±2 2.3	61.9 ± 29.3	70	48.7 ± 30.3	57/59	50.0±31.7	50.3 ± 32.3
ADL	72	87.2 ± 16.5	65	85.4±1 7.4	86.4 ± 17.6	71	75.8 ± 24.2	57/59	77.3±22.4	80.0 ± 21.2
QOL	72	56.2 ± 23.9	65	56.9±2 5.2	59.8 ± 24.6	71	47.3 ± 27.0	57/59	47.7±25.4	52.4 ± 26.6
Other symptoms	72	83.7 ± 14.0	65	80.3±1 6.1	80.9 ± 18.0	71	72.2 ± 19.5	57/59	73.7±18.4	74.8 ± 18.5
KOOS Responder[c]	72	87.5%	65	83%	80%	69	68%	57/59	60%[b]	72%

[a] The number of patients (n) at Year 3 was =57 and at Year 5 was =59

[b] 6 enrolled Extension microfracture patients missing data at Year 3 (0 missing in MACI)

[c] KOOS Responder: A KOOS responder at was defined as a patient who responded to treatment at the particular scheduled visit with at least a 10-point improvement from baseline in both KOOS Pain and Function (Sports and Recreational Activities) scores.

Thank you for allowing us to comment on the analysis, and for your consideration of Autologous Chondrocyte Implantation. ACI offers physicians a viable option for first line treatment of larger lesions, as well as for chronic lesions where other treatment options have not done well.

[redacted]

ICRS
International Cartilage Repair Society

To Whom It May Concern

The U.S. Food and Drug Administration approved MACI® (autologous cultured chondrocytes on porcine collagen membrane) for the repair of symptomatic, full-thickness cartilage defects of the knee in adult patients on December 13, 2016. MACI is the first FDA-approved product that applies the process of tissue engineering to grow cells on scaffolds using healthy cartilage tissue from the patient's own knee. Celia Witten, MD, PhD, the deputy director of the FDA's Center for Biologics Evaluation and Research, stated in a press release that "Different cartilage defects require different treatments, so therapy must be tailored to the patient. The introduction of MACI provides surgeons with an additional option for treatment."

MACI is a viable and reliable option for surgeons to treat patients with large, symptomatic chondral defects. While the number of patients that fit into this category is not large, for many surgeons around the world, MACI provides a valuable treatment when that patient arrives in their office.

A recent systematic review by Elizaveta Kon and her team from the Rizzoli Orthopaedic Institute (*Sports Med Arthrosc.* 2017;25:10-18) focused on the published failure rates of autologous chondrocyte implantation (ACI). Whether with ACI (n=1974) or matrix-assisted autologous chondrocyte transplantation ([MACT]; n=1493 patients), the overall failure rate was 15% over a mean follow up of 7.2 years; with the third generation (MACT, including MACI) having a lower 10.4% failure rate. Even though failure rates reported in this study are relatively low with ACI, they may be higher than those with other cartilage repair procedures used to treat less challenging lesions (i.e., discreet, focal lesions), likely because ACI is often reserved to treat more challenging lesions, such as early OA, degenerative lesions, and large chronic lesions that have failed multiple treatments.

I have personally used ACI (Carticel®) in my practice for the last 20 years with success that both my patients and I are happy with, and my clinical experience echoes the outcomes of this publication.

In closing, I would like to emphasize that MACI is an appropriate option for surgeons to treat patients with large lesions and challenging cartilage problems, who would not fare as well with an alternative treatment option.

Thank you for your consideration and support for cell-based therapies.

Autologous chondrocyte implantation: addendum to previous reports [NICE appraisal ID686]

Produced by Warwick Evidence

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Declared competing interests of the authors

The authors have no conflicts of interest.

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We thank Professor Knutsen for clarifying some aspects of the 2016 paper from the trial he led, and Professor Sally Roberts for additional data from the ORKA study. We thank Professor Leela Biant and Mr Tim Spalding for orthopaedic advice.

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1 SUMMARY

Since autologous chondrocyte implantation (ACI) was last considered by NICE in 2015, some new evidence has become available and is reviewed in this report. In terms of clinical effectiveness, the key points are:

- Age alone should not be a contra-indication to ACI – the key issue is whether there is osteoarthritis;
- ACI has been shown to be effective in teenagers (currently not covered by the NICE scope);
- A new long-term follow-up after microfracture (MF) reports 46% with poor outcomes at 10-14 years (Solheim et al, 2016);
- There is more evidence on enhanced microfracture but not yet long-term data;
- Two good quality reviews looked at return to sport after injury, and found it to be higher after ACI than MF (84% versus 75% and 82% versus 58%) but that return after ACI took much longer; and
- A new UK study with long-term results of ACI has been published by Dugard and colleagues (2017).

The most important new evidence is the 15-year data on microfracture from the trial by Knutsen and colleagues (2016). This trial compared MF with ACI but as is usual with older trials, the ACI was done in people who with chronic cartilage defects who had had previous attempts at repair, both of which reduce its effectiveness. The microfracture results from the Knutsen et al trial are better than was expected from previous studies. They have the longest follow-up of microfracture.

Three new cost-effectiveness studies have been published, but two look only at short-term costs and outcomes and do not provide costs per quality-adjusted life year (QALY). The third is an update of the modelling done by SoBi for the NICE appraisal.

New modelling results from Warwick Evidence were in line with our previous report. The results showed that although ACI was more expensive, it generated more QALYs. MF was less costly, but provided fewer QALYs. ACI appeared to be cost-effective compared with MF, most likely due to the duration of benefit and the likely avoidance or postponement of a second repair or knee replacement surgery. The deterministic incremental cost-effectiveness ratio when comparing MF as a first procedure with ACI as a first procedure was approximately £8,000 per QALY gained. These results were confirmed by the cost-effectiveness acceptability curve.

An important limitation is that data from most long-term studies of ACI do not provide data on the effectiveness of ACI as the primary repair procedure, when it is more effective.

Conclusion

We have reviewed new evidence, which gives mixed messages. The 15 year data from one of the landmark trials, by Knutsen and colleagues challenges our previous assumption that most MF fails over time. However, the Solheim et al study suggests a higher MF failure rate.

We will never have an RCT in which patients are randomised to ACI or MF and followed for 20-30 years to see how many require TKR. And if we did, the results would be obsolete because the technology would have moved on. So decisions have to be made on the imperfect evidence that we currently have.

2 BACKGROUND

Autologous chondrocyte implantation (ACI) in the knee was considered by NICE in 2015 and an Appraisal Consultation Documentation (ACD) was issued in March of that year. After consultation, NICE decided that further analysis was required, and Warwick Evidence was asked to provide this. A second assessment report was provided in March 2016. Unfortunately due to pressure of work at NICE, this has not yet been considered by the Appraisal Committee, and in the interim, significant further evidence has been published. This report takes note of publications found by searches up to 14th May 2017.

Reasons for the uncertainties in this appraisal have included;

- Evolving technologies – ACI is now in its third generation, known as matrix-associated ACI (MACI)
- Follow-up in the clinical trials had been relatively short for a procedure that aims to provide benefits for decades
- The longest follow-up comes mostly from earlier, now superseded, generations of ACI
- There were few long-term follow-up studies of the main comparator, microfracture (MF)
- Microfracture is evolving with new approaches being explored, such as the addition of collagen caps
- There have been no randomised controlled trials (RCTs) comparing characterised ACI against non-characterised ACI. Characterisation aims to select chondrocytes likely to give better quality cartilage.
- The earlier studies of ACI were mostly in patients with chronic cartilage injuries that had not responded to previous attempts at repair, such as microfracture. It is known that ACI is less successful in such patients.

Although follow-up in the trials was quite short, there are long-term observational studies of ACI, though many patients in these received earlier generations of ACI. To recap, the first generation involved injecting the cultured chondrocytes under a cap of periosteum harvested from the patient's tibia – ACI-P. This causes two problems. Firstly, there was some discomfort from the harvest site. Secondly, there was often some overgrowth in the implanted site which had to be removed in a later surgical procedure. This overgrowth can occur with all forms of ACI but is more common with ACI-P.

The second generation used an artificial collagen cap over the cells instead of the periosteal one – ACI-C. The third generation uses a collagen 3 dimensional matrix into which the cells are loaded – MACI.

There have been very few trials comparing ACI-P with MACI. However one trial by Gooding et al[1] compared ACI-P with ACI-C. They found little difference in success rates but reported that ACI-P required further follow-up procedures, as outlined above. Bartlett et al[2] compared ACI-C with MACI and concluded that MACI was slightly better but not statistically significantly so, in a study with 91 patients across both arms.

The NICE Appraisal Committee therefore asked for further modelling using the assumption that the long-term results of MACI would be no worse than those of ACI-P. This is a conservative assumption.

The March 2016 assessment report by Warwick Evidence included survival analysis based on the longest-term data from the trials, and data from observational studies, including the large follow-up study by Nawaz and colleagues.[3] Unfortunately most of the data on survival was from studies in ACI, with much less on microfracture.

Many survival curves were produced, but the likeliest scenario for microfracture was thought to be early success and then steadily accumulating failures that would lead to a long-term need for knee replacement. A similar assumption is made in the study by Elvidge and colleagues[4] from Bresmed, which is the published version of modelling done for the submission from SoBi, the manufacturer of ChondroCelect.

Economic modelling based on this scenario suggested that ACI would be cost-effective, especially in patients with recent cartilage injuries and no previous repair attempts.

Note that neither of the two commercial products being appraised by NICE has a current European marketing authorisation. ChondroCelect was being distributed by SoBi, but because of poor sales it was returned to TiGenix, who withdrew it. The authorisation of Vericel's MACI was suspended in June 2016 because of the lack of a manufacturing site. MACI was approved by the FDA in December 2016.

3 NEW EVIDENCE - CLINICAL EFFECTIVENESS

We have had auto-alerts running since the last assessment report, which was written in early 2016 and submitted in March, and an updated search was done on 14th May 2017. Time does not permit a full review of all new studies so we have selected some publications that provide new data on;

- Long-term outcomes of microfracture, from the 15-year follow-up of the trial by Knutsen and colleagues.[5]
- Results of ACI in younger patients, mainly from the review by Chawla and colleagues.[6] The NICE scope for this appraisal specifies adults with cartilage defects, presumably because the marketing authorisations do not cover younger patients.
- Results of ACI in older patients. It has been reported that ACI was less successful in older patients, including from the UK, by the Stanmore group.[7] However, an analysis by Filardo and colleagues[8] challenges this.
- A tool developed to predict which patients would do best after ACI. The Dugard study[9] uses data on 170 patients and provide success rates, albeit from a single centre of excellence with 83% of operations done by one surgeon.

3.1 Older patients

Filardo et al[8] suggest that the consensus against cartilage repair in older patients should be challenged for three reasons. Firstly, poorer results reported by some studies may have included subjects who were not just older, but had osteoarthritis (OA). Secondly, older people receiving ACI may be less active and so put less strain on the repair. Thirdly, much of the consensus against repair in older patients may be based on results of marrow stimulation procedures such as microfracture, and those results may reflect an ageing bone marrow, and may not apply to ACI. Filardo and colleagues therefore analysed results in their series of 157 patients treated with MACI, after excluding any with OA (Kellgren-Lawrence grades 3-4). They divided the patients into those aged under 40, mean age 26, and those over 40, mean age 46. After adjustment for other prognostic variables, Filardo and colleagues concluded that although results in the under 40s were better, the over-40s also benefitted from ACI. When function scores were compared against people in each age group with healthy knees, there was no difference in relative benefits. This is in contrast to comparing functional results in younger and older ACI recipients. Failure rates at 10 years were similar; 11% for under-40s at ACI and 14% for over-40s. Filardo and colleagues therefore argue that age alone should not be a contra-indication to MACI.

Future ACI may be different and use another technology which is even more robust to the age of the patient. Another recent study by Mumme et al[10], albeit with only 10 patients to date, shows that cartilage can be grown using nasal cartilage chondrocytes, which may retain chondrogenic potential better with age than knee chondrocytes.

3.2 Younger patients

The inactive marketing authorisations for ChondroCelect and Vericel MACI both commented on the lack of evidence in children and adolescents, but more evidence has emerged. Chawla and colleagues (2015)[6] identified 13 studies for their review of cartilage repair in "the paediatric knee" (mean ages ranged from 14 to 19 so "teenage knee" might have been better). Six of these studies involved ACI: three ACI-P, two MACI, and the other a mixture of ACI-P, ACI-C and MACI. Unfortunately, all were case series, mostly with short follow-up. Two had over 5 years of follow-up. If we apply the inclusion criteria used in our second assessment report on ACI (at least 40 patients in case series and 5 year follow-up), none of the studies identified by Chawla et al[6] would be included. The main conclusion from the Chawla review[6] is that microfracture gave poorer outcomes in lesions >3m^2 and had shorter durability.

One further study has appeared, but it is another single centre (and single surgeon – Tom Minas, one of the world leaders) case series of 27 patients.[11] It did have good follow-ups at 5 and 10 years (median FU 13 years, range 2-19). The average age at ACI was 16 (range 13-17). Most knees had had previous procedures, mostly bone marrow stimulation such as microfracture, or debridement. Most had other procedures at the time of ACI. Most of the teenagers got good results – 89% survival rate at 10 years - with only three failures, all within 3 years of ACI.

3.3 Failure rates after ACI

In March 2017, Andriolo and colleagues from the Bologna group published a systematic review of failure after ACI, drawing on 58 articles, published by October 2016, with 4,294 patients.[12] The articles provided data on all three generations of ACI, grouping ACI-P and ACI-C as ACI, and comparing those with MACI. Most studies defined failure as a need for further surgery. Failures rates were 13.7% (lower 95% CI 12.1%) with ACI at mean follow-up of 92 months, and 10.4% (upper 95% CI 12.0%) with MACI at mean follow-up of 80 months, which allowing for different follow=up periods and years of trials, suggest no important differences. Most (64%) failures occurred in the first 12 months, 26% in years 2-5, and 10% after the fifth year.

3.4 Failure after MF

Solheim and colleagues[13] report results 10-14 years after microfracture in a prospective cohort of 110 patients. 46% had a poor outcome, defined as needing knee replacement or a Lysholm score under 64. Symptom scores did improve from baseline but few had normal knee function. 39% had additional surgery. Poor outcomes were predicted by mild OA at baseline, previous meniscectomy in the other knee, a duration of symptoms before MF longer than 3 years, and a poor baseline symptom score. Gender did not affect outcomes.

The 15-year results of the trial of MF versus ACI-P by Knutsen and colleagues have been published, and merit a separate section (Section 5).

3.5 Trials versus routine care

An interesting study by Foldager and colleagues[14] used data from 2,690 patients in the Genzyme/Sanofi MACI database. Sanofi were the original manufacturers of the MACI now marketed by Vericel. Sanofi sold their Cell Therapy and Regenerative Medicine business to Aastrom Biosciences, along with manufacturing centres in the USA and Denmark. Aastrom changed their name to Vericel. Foldager et al compared data from the Sanofi database of MACI used in routine care, with data from trials. Their main finding was that defect size in trials was significantly smaller than in routine care – 4.95cm^2 versus 5.64cm^2 ($p = 0.001$). In routine care, 11% of defects were >10cm^2. However, the difference varied considerably amongst countries, with mean defect size in England being 5.0cm^2, similar to the trials.

3.6 Enhanced microfracture

When we last looked at the evidence on enhancements such as capping microfracture, such as AMIC (autologous matrix-induced chondrogenesis) there were no long-term studies.[15] A small RCT by Volz et al[16] now provides some additional 5-year data comparing three groups; microfracture alone (13), or MF with a collagen cap (ChondroGide) either glued (17) or sutured (17) in place. Randomisation used sealed envelopes. Recruitment proved difficult because patients did not want to be randomised, and only two of the original seven centres continued to five years follow-up, with a total of 39 patients. Mean defect size was 3.6cm^2, range 2.1 to 6.6cm^2. In symptoms and function, all groups improved by 2 years, but improvement was sustained better at 5 years in the capped group. Defect filling assessed by MRI at 5 years showed better filling in the capped group. The trial (NCT02993501) was funded by Geistlich Pharma, the manufacturers of Chondrogide.

A similar earlier trial by Shive and colleagues[17] also reported 5 years results of capped MF, using the BST-Cargel scaffold, reported improved MRI filling compared to MF alone, but there was no difference in symptoms: Western Ontario and McMaster Universities Osteoarthritis (WOMAC) or Short-Form 36 (SF-36).

We therefore await long-term data on "enhanced microfracture".

3.7 Return to sport

One very useful outcome measure is return to sport. Many people with chondral defects are sportsmen or women.

Campbell and colleagues[18] provide a high quality systematic review (admittedly of mostly low-level studies with only one RCT) of return to sport by both amateur and professional athletes. The proportion returning was higher with ACI than MF – 84% versus 75% ($p<0.01$). In professional athletes, clinical outcome scores were similar at 2 years follow-up but were significantly ($p = 0.005$) better in the ACI group at 7.4 years, because they were stable in the ACI group but declined over time in the MF group. However, return was much faster after MF (return to athletics by 3-6 months) than after ACI (10 to 18 months).

In another good quality review, Krych and colleagues[19] came to similar conclusions, probably because they used most of the studies used by Campbell et al, though they added as many more. Campbell et al included 20 studies whereas, Krych et al included 44. The Campbell review was rather more focused on high level athletes including professionals, where the Krych review was mainly in recreational sports people, and for more recent years (1998-2016). The inclusion criteria were slightly different. Krych et al concluded that 82% returned to sport at some level after ACI compared to 58% after MF. The Krych review does not give a comparison of persistence at sport over time, but they point out that with an average age of 35, some people may be reducing activity because of age rather than cartilage (the median age in the Campbell review was 28.6 years.).

3.8 Quality of cartilage repair

A 2016 systematic review by DiBartola and colleagues[20] set out to assess the correlation between histology of the cartilage repair, and clinical outcomes, but it also reported poorer histological outcomes after microfracture compared to ACI. However, there were only six studies of MF compared to 30 of ACI.

3.9 Key points from review of recent clinical effectiveness studies

- Age alone should not be a contra-indication to ACI.
- ACI has been shown to be effective in teenagers (currently not covered by the NICE scope).
- A new long-term follow-up after microfracture reports 46% with poor outcomes at 10-14 years (Solheim et al).
- A new systematic review of failure rates (defined as a requirement for further surgery) after ACI reports little difference amongst the generations.
- A registry-based study reported that in some countries, chondral defect size in routine care was larger than in the trials. This did not apply to England.
- There is more evidence on enhanced microfracture but not yet long-term data.
- Two good quality reviews looked at return to sport after injury, and found it to be higher after ACI than microfracture (84% versus 75% and 82% versus 58%) but that return after ACI took much longer.

4 NEW EVIDENCE – COST-EFFECTIVENESS

4.1 Systematic review of new economic studies for autologous chondrocyte implantation: update

The updated search for any existing economic evaluations from July 2014 to May 2017, identified three cost-effectiveness studies: Elvidge et al (2016)[4], Miller et al (2015)[21] and Schrock et al (2017)[22]. The first article reported an incremental cost-effectiveness ratio (ICER) in terms of cost per quality-adjusted life year (QALY); the latter two articles did not present cost per QALY. Hence, the first article is described in more detail below.

In brief, Miller et al (2015)[21] estimated the cost-effectiveness of microfracture and osteochondral autograft transplantation (OAT) by developing a cost model using three studies identified in the literature review which included data on surgical time, failure rates, revision surgeries, outcome scores, and return to athletics. Cost-effectiveness was reported as cost per point change in symptom and function scores. The authors found that MF was more cost-effective when comparing Lysholm and Hospital for Special Surgery (HSS) scores, but OAT was more cost-effective when comparing Tegner and International Cartilage Repair Society (ICRS) scores. There was also a significantly lower cost for return to play in athletes after OAT compared with MF. However, no consideration was given to long-term outcomes such as knee replacement, and no costs per QALY were estimated.

Schrock et al (2017)[22] estimated the cost-effectiveness of MF, OAT and ACI-1. In a secondary analysis, they also compared the functional outcomes of MF, OAT, ACI-1, and ACI-2. ACI-1 was ACI-P, and ACI-2 appears to be MACI. The literature review identified 12 studies using the Lysholm, International Knee Documentation Committee (IKDC), Knee injury and Osteoarthritis Outcome Score (KOOS), and/or HSS Knee Score. A weighted mean difference in pre- to post-operative functional outcome score was calculated for each treatment. Mean per-patient costs associated with the three treatments were obtained from literature review based on a national private insurance database. The change in functional outcome score was significantly greater for ACI-2 when compared with all other treatments. The cost-per-point change in functional outcome score was $200.59 for MF, $313.84 for OAT, and $536.59 for ACI-1. No costs were provided for ACI-2, and so no cost per point was derived. No long-term modelling was done and no costs per QALY are estimated.

4.2 Elvidge et al (2016)

Elvidge et al (2016)[4] is an updated version of the economic model and commentary by SoBi which was summarised in Chapter 5 of the HTA report.[23] The update takes account of discussions at the Appraisal Committee meeting. For convenience, the main commentary from the HTA report has been reproduced here with any amendments (based on the NICE assessment process), superseding the text in the HTA report.

Introduction and model structure

The economic analysis by SoBi used a *de novo* Markov model to assess the cost-effectiveness of characterised chondrocyte implantation in relation to microfracture from an NHS and Personal Social Services (PSS) perspective. Both costs and outcomes were discounted at a rate of 3.5% per annum in line with NICE guidelines.

Microfracture was considered to be the only relevant comparator for ACI and other comparators such as mosaicplasty were not considered for this analysis – this is a reasonable assumption. The model is similar to the Warwick assessment group model where patients enter the model at the time they receive the procedure (ACI or MF). However, there are differences between the Warwick model and the Elvidge model: the cycle length used in the model is 1 month, whereas the Warwick model used a cycle length of one year. The median age of patients receiving a procedure in the Elvidge model is 33 years and the model has time horizon of 75 years (lifetime). The model is separated by gender. Past evidence suggested that there is no difference in the success or failure of the two different procedures if lesions are comparable.[24] However, recent work from Oswestry by Dugard and colleagues[9] on developing the ORKA tool has found a greater failure rate amongst women, though this is as yet from a single centre (and with most patients treated by one surgeon) with only 26 failures requiring arthroplasty.

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

Patients who receive best supportive care (BSC), may deteriorate and are assessed for a total knee replacement (TKR). The model assumes that a patient can only receive up to a maximum of three TKRs. The model assumes that patients can die at any stage from all-cause mortality, and there is a low risk of mortality from undergoing a TKR or a TKR revision.

Model inputs

1. Efficacy of first treatment

The model uses time to treatment failure (TTF) as a proxy measure of treatment efficacy (i.e. when a new procedure for the same defect was required). This information on time to treatment failure of MF (i.e. transition probability for moving from primary treatment success to treatment failure) was obtained from Kaplan-Meier plots as reported in the Vanlauwe et al (2011) article.[25] This article reported that ACI was better than MF and that patients in the ACI group waited longer before needing a further procedure due to the longer benefits. This is a reasonable assumption for the model.

As no data was available for ACI failure beyond 5 years, a literature search was performed for trials with more than 5 years of data for ACI. Five papers were identified[26-30] and data were extracted from the Kaplan–Meier graphs in the papers, using the algorithm from Guyot et al[31] and pooled. This is reasonable method of pooling. Parametric survival curves were fitted to the data, and the Gompertz curve providing the best fit based on both the Akaike information criterion and visual inspection.

2. Subsequent treatment

The model in the base-case analysis assumed, based on clinical advice, that when ACI fails that 90% of the patients will receive MF and when MF fails that only 5% of patients receive another MF. The paper did not say why patients who receive a first MF are less likely to receive second MF compared to patients who receive an ACI first.

The model used the failure rates for subsequent MF from the Vanlauwe et al (2011) article which reported MF failure rate of 16.4% at 5 years (converted monthly rate 0.30%).[25] The model assumed, based on clinical advice, that a second MF following a first MF would be half as effective i.e. twice the failure rate, therefore the failure rate was doubled to 0.6% per month.

Forster et al[32] reported a failure rate for debridement of 20.0% at 1 year (converted monthly rate was 1.84%) which was used for BSC following initial and subsequent treatment failure in the analysis. Failure of BSC leads to knee replacement.

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

3. Mortality

Office of National Statistics[33] data was used for all-cause mortality (split by age and gender) and for the base-case TKR mortality data this was based on a figure reported on the NHS Choices website (1.6%).[34] The model assumed that the mortality rate for TKR revision would be 2.5%.[35] This is a reasonable assumption, as this is a longer operation, patients are older and rehabilitation might be slower.

4. Costs

Costs were reported in 2014/2015 prices. The costs for the different procedures, rehabilitation, TKR, TKR revisions and pain relief were obtained from UK sources, literature and the HTA report by Clar et al.[36] The cost of procedures included the costs of surgery, inpatient stays and physiotherapy follow-up. The cost of TKR was identified from the NHS reference costs[37] and the costs for TKR and TKR revision (£5,524 and £12,714, respectively) look correct. The cost for MF was costed as an inpatient procedure (£2,963), but it can be done as a day procedure.

The cost of ACI included the cost of the product including two-way courier and cell culture (£16,000) plus the cost of arthroscopy and cell harvest (procedure 1 - £870) and arthrotomy conducted in an outpatient setting (procedure 2 - £2,396). (We think this latter cost means day case rather than outpatient, but the cost is too high for that, so perhaps an overnight stay is included).

The model also included the cost of rehabilitation after ACI, MF and TKR in line with the Warwick model. In addition, the model also included the cost of pain relief medication – which consisted of paracetamol (this cost was not included as the patients would have purchased this over the counter) and non-steroidal anti-inflammatory drugs (NSAIDs). This was a weighted average cost for NSAID per month as £5.58. This cost is negligible and has not been included as a cost in the Warwick model.

The model also included a cost for patients who were classed as "unresolved patients". This cost was estimated at £34 per month which included the cost of GP visits, treatment visits, medications, outpatient visits, physiotherapist, prescribed aids (not specified but presumably walking aids), complementary (not specified) and other therapies. This total cost was based on patients with lower limb osteoarthritis, but for some patients this cost may be an over-estimate as some of these patients may just have pain relief medication and choose to put up with the pain.

5. Health-related quality of life

Utility scores were based upon on analysis of the SF-36 questionnaires which were collected during the TIG/ACT/01 trial and were mapped to EQ-5D values using a mapping algorithm.[38] These are plausible utility values. The model also accounted for the decreasing utility over time by using age-related UK population EQ-5D weights as reported by Kind et al.[39] The model assumed that after successful ACI and MF, patients would have the same benefits, and the utility value used after surgery was 0.73. The model stated in the sensitivity analysis that the treatment benefit lasts for the duration of the trial period – approximately 5 years. The model also does not take into account that after MF the utility value will stay at this value for a few years but is likely to decline later, eventually to the pre-surgery value as these patients are most likely to require another repair.

6. Adverse events

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

Model results

The total discounted cost of ACI was £23,307. The total cost of MF was £8,008. Total QALYs gained for ACI compared with MF were 0.72. The ICER for ACI compared with MF was £21,245 per QALY. The main cost drivers were the cost of the cells and the fact that fewer people needed further repair or TKR with ACI compared with microfracture. The model also assumed that there were QALYs losses by ACI patients when they received a subsequent MF (-0.61 less QALYs when looking at QALY results disaggregated by health state), compared to MF patients when they received a subsequent MF (as patients who receive microfracture will fail more quickly).

The sensitivity analyses found that the ICERs for the different efficacy scenarios and the subsequent treatment efficacy scenarios were consistent with the base-case analysis; that is, although ACI was more expensive it was also more effective. The ICER was sensitive to the model time horizon. For

example, if a 5-year time horizon was used i.e. 5 years the resulting ICER was approximately £275,000. This was due to the majority of costs of ACI being incurred upfront i.e. in the first few years and the benefits from ACI not being seen till later i.e. fewer people moving to an unresolved state and fewer people in need of a TKR. The model became cost-effective when the model when the time horizon was 45 years (ICER approx. £24,000). The ICER was robust to other scenarios which were tested such as different utility values, TKR mortality and discounting. The probabilistic sensitivity analysis results were similar to the deterministic results.

In our first assessment report, we commented that the model assumptions and results looked plausible. However (as with the AG modelling in our second report) a key assumption is that there is progressive failure of microfracture. This is illustrated in Figure 3 of the Elvidge et al (2016)[4] study, where almost all MF is shown to fail over time, whereas only half of ACI fails. This key assumption is challenged by the Knutsen et al (2016)[5] results, showing better results for microfracture than for ACI. From Figure 3 of the Elvidge study, the predicted 15-year failure rate after MF (failure being defined as requiring further surgery) is just under 50%. From Figure 2 of Knutsen et al (2016) study, the observed failure after MF is 38%. However, it is what happens after 15 years that is *more* important. Elvidge and colleagues (2016) assume a continuing fall in MF survival, whereas the Knutsen et al (2016) graph could suggest a plateau. We lack data as to which is correct.

5 THE KNUTSEN 2016 RESULTS

The long-term results of the trial by Knutsen and colleagues[5] have caused controversy. The ACI results are poorer than some more recent studies. This is perhaps not surprising, given that the trial was done in the early years of ACI, in patients with chronic defects (mean 3 years) who had had previous attempts at repair. Fu and Soni[40] in their commentary on the results suggest that the poor ACI results could be due to damage to the subchondral plate.

Minas and colleagues[41] provide a commentary on behalf of the ICRS. They make a number of points about size of chondral defect (ACI is more effective for larger lesions), the learning curve in the early days of ACI, the high prevalence of osteoarthritis in the 15-year Knutsen results, and the contrast between the Knutsen results and other more long-term studies of ACI reporting much higher success rates.

However, the striking aspect of the Knutsen trial is the success of microfracture, which is quite different from other studies. In the huge study by Layton et al[42] in 2,948 patients receiving microfracture (after excluding the older Medicaid and Medicare groups), 8% were failures after 1 year, 16% after 3 years and 31% after 5 years. The Knutsen trial reports only 38% failures, 15 years after MF.

5.1 New studies with time to event analyses

In the interval between completing the last AG report (March 2016) with the extra analyses requested by NICE and the next Appraisal Committee meeting new relevant data have become available. As reported in Section 3, the AG updated the literature search and identified new studies, the most important of which is Knutsen et al (2016)[5] describing the 15-year results from the RCT comparing MF versus ACI, first described in 2004.[43] It provides the only available time to failure data for MF, from an RCT that extends beyond 5 years, and so provides very important data.

The results reported are in conflict with the tentative conclusions of the March 2016 AG report that suggested clinical superiority for ACI relative to MF based on parametric modelling of failure beyond the observed data. This section includes:

[A] analysis and assessment of the Knutsen et al. RCT based on the 2016 paper, helpful contact with the first author, and information on the earlier 2-year and 5-year follow up papers together;

[B] analysis of other newly identified studies with time-to-event analysis of treatment failure again enhanced by contact with authors. One of these studies, Dugard et al (2017)[9], is the only study with failure data for UK patients other than that of Nawaz et al (2014)[3] employed in the AG's economic analysis.

[C] Consideration of the implications of the new studies for economic modelling.

[A] Knutsen et al (2016) RCT

The 2016 Knutsen publication follows earlier 2-year [43] and 5-year [44] reports of results. Forty patients were randomised to MF and forty to ACI. Randomisation was described as follows: "*With use of sealed envelopes, patients who fulfilled the inclusion criteria were randomized during the arthroscopy to be treated with either autologous chondrocyte implantation or microfracture*".[43] Communication with the lead author confirms that block randomisation was employed with blocks of ten patients allowing equal numerical balance between arms. Sealed envelopes were used for allocation concealment. Surgery was undertaken in four centres. MF was done by the Steadman method, and ACI was performed according to technique of Brittberg et al (1994).[45]

Some baseline characteristics for each arm were reported in the Supplement to the 5 year paper and are reproduced below. There was reasonable balance between arms but there was no indication of variance or normality of distributions.

TABLE E-2 Baseline Patient Characteristics

	Autologous Chondrocyte Implantation	Microfracture
Mean age *(yr)*	33.3	31.1
Mean defect size *(cm^2)*	5.1	4.5
Mean no. of previous operations	1.6	1.4
Mean weight *(kg)*	81.0	82.1

Other characteristics conformed to study inclusion/exclusion criteria and are shown below.

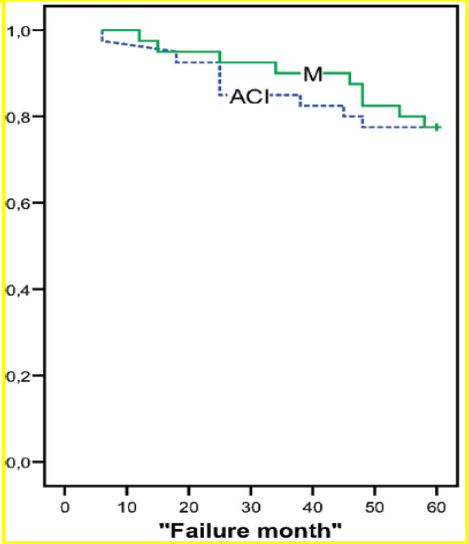
TABLE E-1 Inclusion and Exclusion Criteria
Inclusion Criteria
Age of 18-45 years

The patient had to understand the rehabilitation protocol and be willing to follow it
Isolated Outerbridge grade-3 or 4 defect on the medial or lateral femoral condyle or trochlea
Size of defect of 2-10 cm² after débridement to healthy cartilage. Osteochondral lesions up to 10 mm in depth
The knee should not be too tight and not have a fixed flexion deformity
The knee should be stable
Only symptomatic lesions are included
Normal standing radiographs made
Exclusion Criteria
s
Degenerative knee conditions: osteoarthritis, rheumatoid arthritis, gout, Bechterew disease, or chondrocalcinosis
Malalignment with >5° valgus or varus compared with normal

Patellofemoral instability
Seriously overweight, defined as body mass index of >30

The 2016 paper states "defects *were relatively large (range, 1.44 to 11.25 cm^2) chronic focal cartilage defects*".[5] How defect size range was disposed between arms was not reported.

Nearly all (80%) of defects were of the medial femoral condyle, and nearly all participants (93%) had received previous knee surgery, for a range of indications, but with 1.6 and 1.4 previous procedures for the defect in the ACI and MF groups respectively. The median duration of symptoms was 36 months. Both duration of defects and previous repair attempts reduce the likelihood of success with ACI. However, most of the early studies in ACI used it after less expensive procedures had failed. Failure was defined as the requirement for further surgery. At 2 years,[43] one and two failures were reported in ACI and MF groups respectively; at 5 years, nine failures were reported for both groups[44] and at 15 years, 17 failures were reported for the ACI arm and 13 for the MF arm.[5] Time to failure Kaplan-Meier plots were presented in both the 5 year and 15 year papers. These are reproduced in Figure 1.



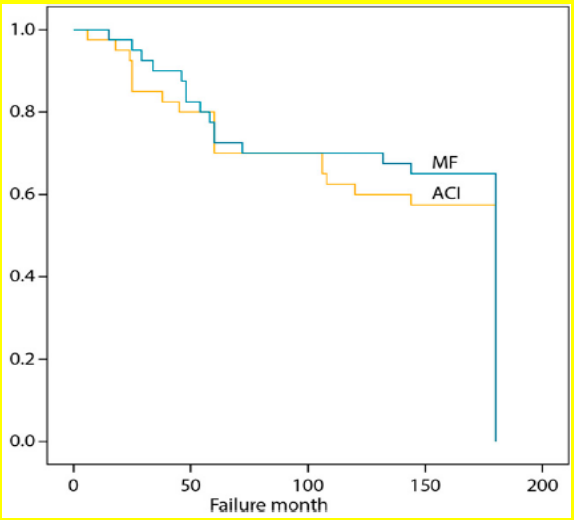


Figure 1: Kaplan-Meier plots from Knutsen 2007 and 2016 papers (copyright protected)

Table 1 of Knutsen et al (2016) presents the year of failure for 17 ACI recipients and for 13 MF recipients (see Appendix 8.2). Patients were enrolled in the study between January 1999 and February 2000[43] but the year or time of intervention was not listed in text or table. The AG assume that interventions were probably mostly received in 1999 with some patients receiving surgery in

2000, probably early in that year. The AG has used the Kaplan-Meier (KM) plots of Figure 2 Knutsen et al (2016) as the preferred source of time to failure data.

5.2 Time to failure KM plots (Knutsen et al)

Taking the vertical steps in the Knutsen 2016[5] and 2007[44] KM figures to represent the times of events the AG used Digitizelt software to itemise the times of failure in the published failure plots. The AG would expect that event times would be nearly the same for data to 5 years irrespective of which plot was being digitised. The AG digital results are summarised in Table 1.

Table 1: Months at which events are depicted in the 2007 and 2016 failure plots

MF 2007 (8 steps)	MF 2016 (13 steps)		ACI 2007 6 steps*	ACI 2016 11 steps
11.6	15.6		5.7	6.62
14.6	25.6		17.6	18.3
24	29.5		24.7	25.6
33.7	34.55		37.7	38.4
45.8	46.6		44.7	45.8
47.65	48.7		47.7	60.3
53.7	54.3			106
57.8	58.8			108.5
	60.5			120
	72.1			144
	132			
	144			
	180			
* Between 5.7 months and 17.6 months the 2007 paper shows a descending diagonal rather than a step				

There were some discrepancies in the AG estimates of the event times when 5 year and 15 year plots were compared. In a few instances these were too large to be easily explained by errors in digitising; these occurred in both MF and ACI arms. It appears that there were some differences in data used by the authors for the 5 year and 15 year plots, possibly due to aggregation of events to some yearly intervals in the 2016 publication, but these are not important. The 15-year plots show prolonged periods during which no events were registered. For the MF arm this zero-event phase extends from ~6 to ~11 years (5 years with no events); for the ACI arm a zero-event phase extends from ~5 years to nearly 9 years (nearly 4 years with no events). The MF plot in particular appears to consist of three distinct phases: 0 to 6 years with regular events, a phase with no events followed by a resumption of events at 11 years to end of follow up. This pattern may be partly explained by early failures having further repair attempts and some later ones having knee replacements due to the development of osteoarthritis.

Ascertainment of outcomes is described in the 2016 15-year paper as follows: "The first author *(G.K.) in collaboration with the surgeons from each center carried out the long-term follow-up evaluation during the period from March 2014 until March 2015 (14 to 15 years after treatment). However, the failure status for all patients was recorded after a minimum of 15 years following the index surgery. Twenty patients who were not able or willing to attend the follow-up evaluation in person were contacted by mail or telephone. Two patients were lost to follow-up".*[5] How much of this applies to the failure outcome is not clear but the AG interpret this as indicating that determining failure events beyond those observed for the 5-year publication may have been undertaken retrospectively rather than prospectively. Also, ascertainment of further surgery may have relied on collaborative discussion between surgeons, and for 20 patients (a quarter of all trial participants) ascertainment may have depended on patients' recall and correct attribution of intervention types received during the period 5 to 15+ years. In such a case the number and precise timing of events may lack total accuracy.

5.3 Reconstruction of IPD using the published Knutsen et al (2016) failure plots

In the 15-year paper thirteen and seventeen failures were reported for the MF and ACI arms respectively. The AG reconstructed individual patient data (IPD) from the KM plots using the method of Guyot et al (2012).[31] The 15-year paper states "*the failure status for all patients was recorded after a minimum of 15 years following the index surgery";* this indicates that all censoring occurred at or after 15 years. In the case of the ACI plot all events occur before 15 years and therefore before censoring. Using the AG's reconstructed IPD for ACI the AG was able to generate an identical ACI plot to that reported (Figure 2 and Appendix 8.3). The depth of the steps in the plot indicated that multiple events coincided at certain times (or at very similar times unresolved in the plot). For example at ~60 months (about 5 years) four ACI failures were experienced. This seems highly coincidental over a 15 year observation period and probably reflects aggregation of events to yearly times in some parts of the plot.

The AG's reconstruction of IPD using the reported number of MF events (13) did not allow the reproduction of the published plot for MF. The published plot has thirteen steps which correspond to the reported number of events, however inspection of the depth of the steps in the MF plot suggests that in fact the steps at about 48 months (~4 years) and at about 60 months (~ 5 years) correspond to two events rather than one (the steps at these times are twice the depth of the other steps). Adopting these values allowed reproduction of the published MF plot (Figure 2 and Appendix 8.3). It appears

possible that the number of MF failures may be misreported (i.e. there were possibly 15 not 13 failures) and aggregation of events at 4 and 5 years may have been implemented.

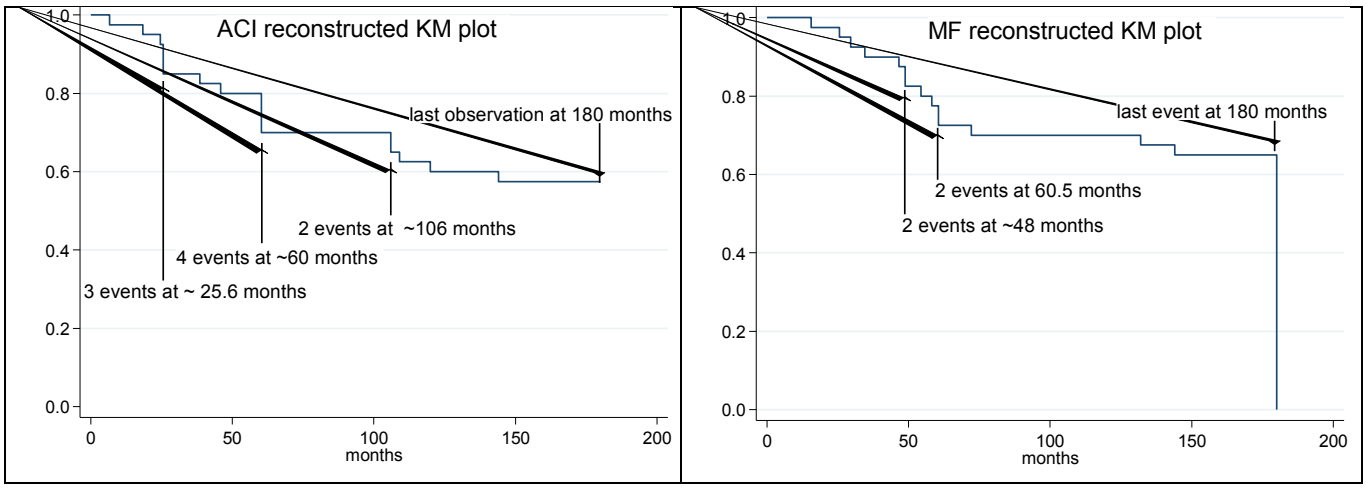


Figure 2: AG reconstructed KM plots based on Figure 2 of Knutsen et al. 2016

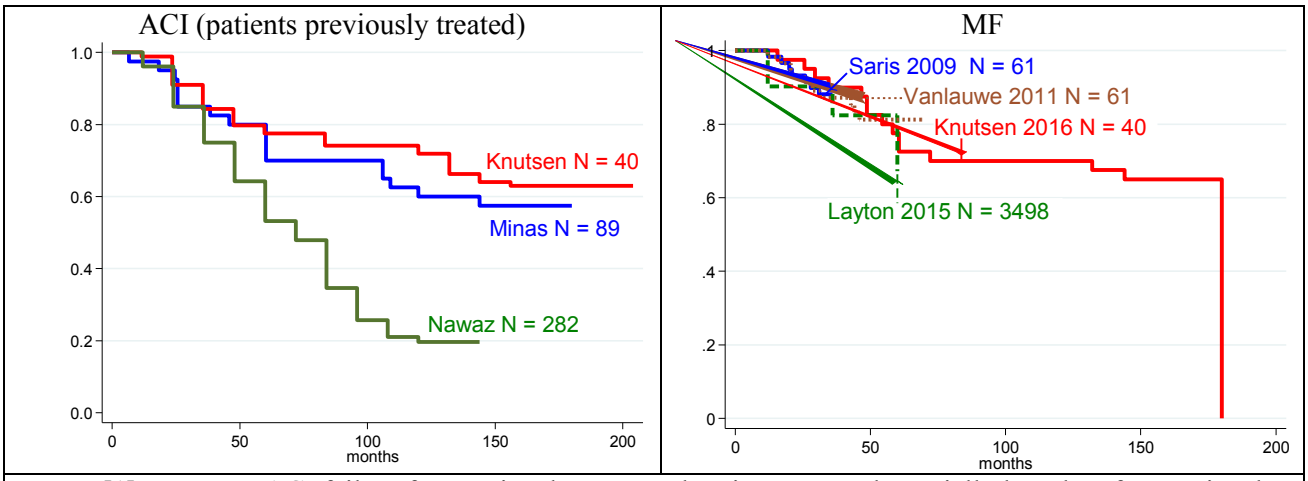
The Knutsen authors' conclusion based on the 5 year data was: "*The results of our study led us to propose that microfracture, a low-cost and minimally invasive procedure, should be preferred as the first-line cartilage repair procedure for defects located on the medial or lateral femoral condyle of the knee. Autologous chondrocyte implantation may be preferred as a second-line treatment, particularly for large defects that are not contained"*. 93% of patients in the study had already received a first line procedure and therefore the AG do not think that the reported evidence is strictly relevant to choice of first line treatment. As noted previously, the early trials of ACI were based on an approach that tried an inexpensive treatment such as microfracture first, and then tried ACI, sometimes as "salvage", and their results are not applicable to a situation in which ACI would be used as primary intervention.

The authors' conclusion based on the 15 year data was stated as follows: "*The risk of treatment failure and the frequency of radiographic osteoarthritis are problematic. Our findings raise serious concerns regarding the efficacy of these procedures in delaying osteoarthritis and preventing further surgery. Continued basic and clinical research is needed in this field"*.

In the context of this conclusion the AG has compared the 15 year ACI failure plots from Knutsen et al (2016) with those reported observational studies that reported time to event data for previously treated knee defects (only studies with time to event data beyond 5 years are considered). It is evident (Figure 3) that the ACI failure results reported by Knutsen et al (2016) are not inferior to those of the two larger observational studies of Minas et al (2014)[30] and of Nawaz et al (2014).[3] It should be

appreciated however that ACI interventions, failure definitions and defect sites were not identical in these three studies.

The AG has compared the reconstructed 15 year MF failure plot from Knutsen et al (2016) with plots based on the results reported in two other MF studies with ≥5-year follow-up (the TIG-ACT trial Saris et al (2009)[46] Vanlauwe et al(2011)[25], and Layton et al (2015).[42] We did not include the SUMMIT trial (Saris et al (2013)) because published follow-up was only for two years. Up to 6 years, the three plots are similar and by visual inspection imply increasing hazard through time, after 6 years the Knutsen et al (2016) plot exhibits a change in trajectory (Figure 3). Of the 61 MF patients in Saris et al (2009), 77% had received previous intervention; this compares with 93% of patients across both arms in Knutsen et al (2016), and an unreported proportion in Layton et al (2015).[42]



Notes: [1] In Nawaz ACI failure for previously untreated patients was substantially less than for previously treated; [2] MF failure in the TIG-ACT trial is shown for both 3 years follow up (Saris 2009) and 5 years follow up (Vanlauwe 2011), because the latter paper had an anomalous risk table in the KM plot which made accurate reconstruction problematical (please refer to original AG report).

Figure 3: Comparison of Knutsen 2016 failure for ACI and MF with that reported in observational studies

5.4 Modelling failure reported in Knutsen et al (2016)

To facilitate cost-effectiveness sensitivity analysis the AG have attempted to model ACI and MF failure reported by Knutsen et al (2016), in order to estimate results over a lifetime. If the mean age at first operation was 33, then the mean age by the 15-year follow up would be 48 years, with perhaps 3 decades of life left.

Parametric models, including flexible models, when fitted to the whole KM plots for ACI and MF failed to produce good visual fits to the data. This was more pronounced for the MF plot. Best fits

are shown in Figure 4 upper panel; their extrapolations to lifetime horizon are shown in the lower panel Figure 4. Lognormal models indicate similar failure trajectories for ACI and MF, flexible models indicate superior performance for MF that contrasts with the AG fit to 5 year data reported in Knutsen et al (2007)[44]; all models are associated with substantial uncertainty. About 50% of non-failures had early OA at mean age of 48 so that pathological changes beyond 15 years might be expected to increase failure rates.

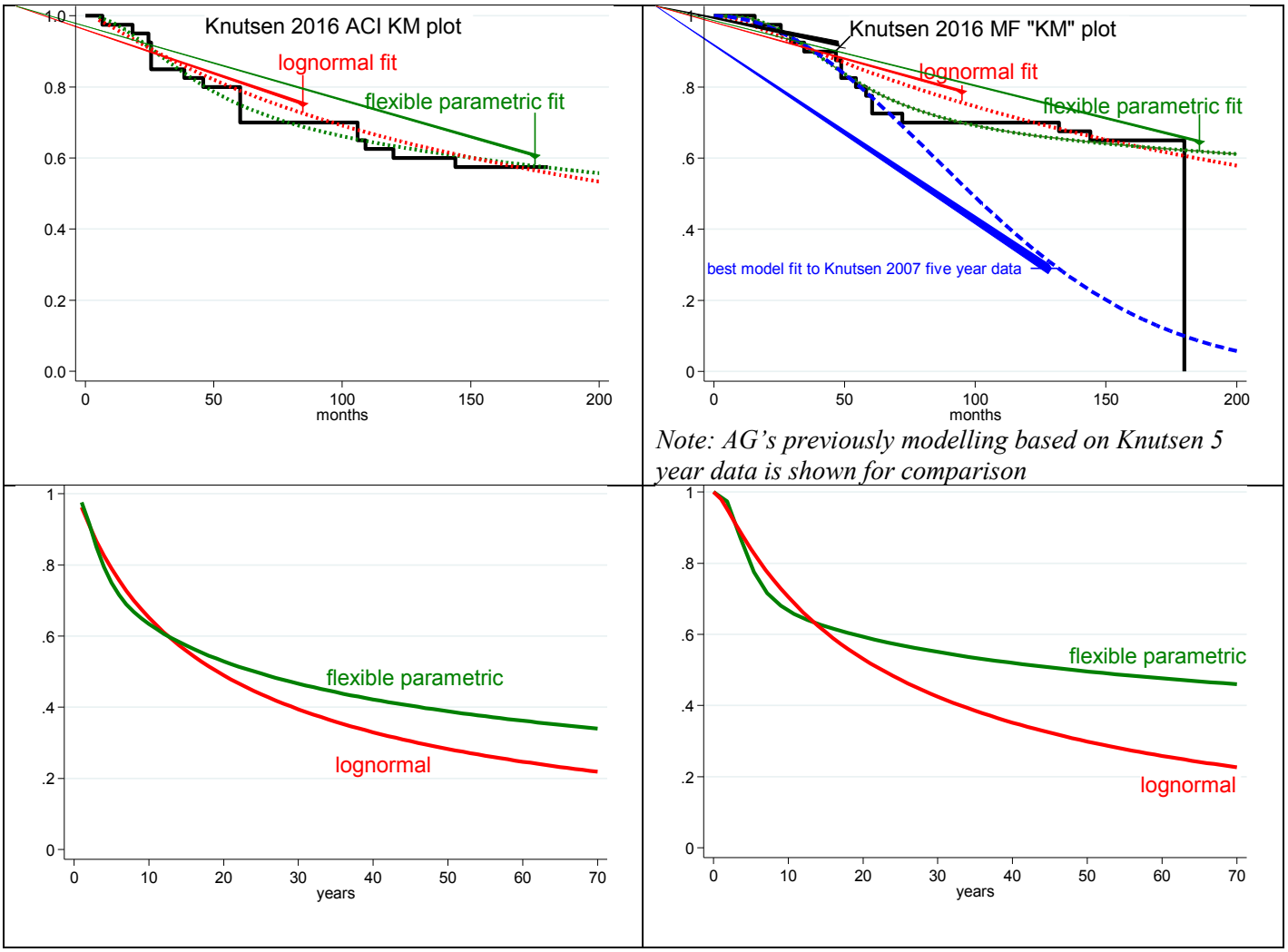
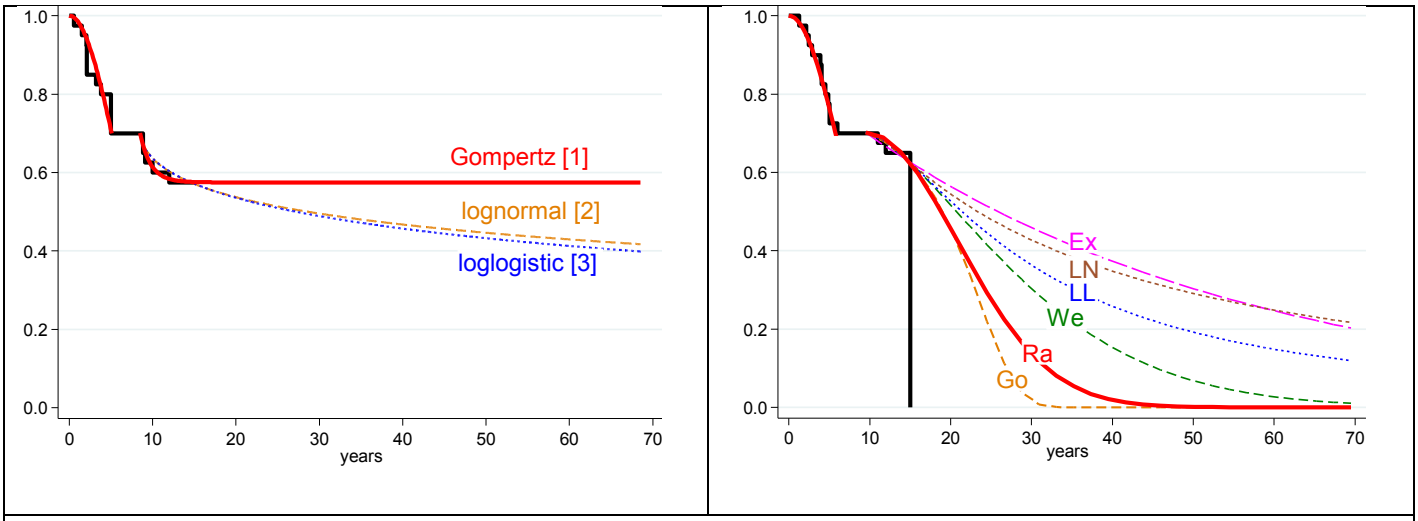


Figure 4: Parametric models fit to the Knutsen 2016 KM data for ACI (left panel) and MF (right panel)

Because of the "three phase" appearance of the KM plots the AG explored piecewise modelling as an alternative additional approach. The initial and late phases were modelled separately; KM data for the no-events phase was interspersed between models. The start time for the third phase was taken as 9 years for ACI and 9.5 years for MF. Information criteria for various piecewise parametric fits are summarised in Appendix 8.4. Appendix 8.5 shows last phase modelling of MF when the start time is

set to 10 years. Because of the small number of events during the late phase, the models can generate widely varying extrapolations. Figure 5 shows the three best ACI piecewise fits (according to AIC and BIC criteria) relative to six fits for MF; these suggest that ACI has a superior long term performance relative to MF. For the MF late phase superior information criteria values were returned by the single-parameter models (exponential constant hazard, and linear increasing hazard) and these bracket nearly all the two-parameter model curves. A Weibull model (which nests exponential and linearly increasing hazard models) may represent a conservative preferred choice.



Left panel: ACI: information criteria (AIC BIC) values for the three best models, best [1], second best [2], third best [3]: Gompertz 44.59 & 4.32, lognormal 46.61 & 49.34, loglog 47.2 & 50.00.
Right panel: Ex = exponential; LN = lognormal; LL= loglogistic; We =Weibull; Ra = Rayleigh (linearly increasing hazard); Go = Gompertz. MF; information criteria (AIC BIC) values for the three best models: Rayleigh 25.04 & 26.37, exponential 25.21 & 26.54, lognormal 26.59 & 29.26

Figure 5: Piecewise models of ACI and MF failure based on Knutsen et al. 2016 time to failure data

In summary, Knutsen et al (2016) present the only time to failure KM result for MF that extends beyond five years. The result suggests that to 15 years ACI and MF are equally effective or equally ineffective interventions for previously treated defects. The authors conclude that this equality also applies for the progression of osteoarthritic degeneration. The AG has made the following observations:

a] After five years the failure events may not have been ascertained prospectively but possibly retrospectively from a perspective of 15 years.

b] Failures may have been ascertained by recall by non-attendee patients (one quarter of study participants contacted by telephone or mail).

c] It may not be possible to be sure that all failure events were ascertained or that their timing is known / reported with total accuracy. This would apply to both arms.

d] The 2016 ACI failure plot is reasonably concordant with the results reported for two relatively large observational studies of previously treated patients (Nawaz et al (2014)[3], n = 282; and Minas et al (2014)[30], n = 89).

e] The Knutsen et al (2016) MF failure plot is consistent with those from two observational studies (Saris et al (2009)[46], n = 61; and Layton et al (2015)[42], n = 3,498) up to ~ 6 years, after which both the MF and ACI Knutsen failure rates plateau.

f] Parts of the Knutsen et al (2016) KM failure plots may represent annualised aggregation of failure events, however it is not certain that this has been applied consistently across the whole time span of the study.

g] Modelling Knutsen et al (2016) failure in order to extrapolate for cost-effectiveness analysis was problematical because of the small study size and the somewhat unusual distribution of events through time. Modelling all the data indicated about equal long-term performance of ACI and MF (lognormal models) or superiority of MF over ACI (flexible parametric models). Piecewise modelling using best fits according to information criteria indicated superiority of ACI over MF; however, for MF only three late events occurred beyond 9.5 years so that piecewise models with very similar performance on information criteria generated extrapolations that differed considerably. Using parsimony as a guide to the best fit suggests that risk of MF failure (hazard) beyond 9.5 years increases through time while that for ACI failure decreases. All models based on Knutsen et al (2016) data are associated with considerable uncertainty because we do not know whether the plateau will continue, or whether as the cohort ages into the range where TKR is more acceptable, failures will increase.

The only long term evidence of failure after MF other than Knutsen et al (2016) comes from single arm studies that did not report time to event Kaplan-Meier plots. Solheim et al (2016)[13] reported that of the 110 patients, 43 (39%) required additional surgery over a follow up of 10 to 14 years. This compares with 13 of 40 (32.5%) in Knutsen et al (2016). Steadman et al (2003)[47] (n= 68) reported only 2 failures (at 2 and 3 years post-surgery respectively) in a study in which outcomes were followed up for 7 to 17 years (mean 11.3 years). This result appears to be a distinct outlier in context of results from other studies. We note the comment by Knutsen and colleagues (2016) that the very good Steadman results were based on only 25% of patients receiving MF at that centre, which raises a question of selection bias.

An alternative published approach[48] (network meta-analysis) to estimating if in the long term ACI is superior to MF is considered in Appendix 8.6.

B] Other new studies with time to event data

Two new ACI observational studies with time to event KM plots were identified: Ogura et al (2017)[11] and Dugard et al (2017).[9] Ogura evaluated ACI in 27 patients aged <18 years old (29 knees; mean age, 15.9 years) and reported a knee success rate (no graft failure) of 89% (95% CI, 70%-96%) at both 5 and 10 years. This study is not considered further here because the NICE scope includes only adults and it is quite small.

Dugard et al (2017) represents the only ACI study of UK patients other than Nawaz et al (2014)[3] (in which the UK studies of Bentley et al (2012)[29] and Biant et al (2014)[28] were subsumed). There were 170 patients of mean age 37.3 ± 9.7 [range 15.1-65.8] and 64% were male; more than 90% had received previous intervention. Further demographic details are presented in Table 1 of Dugard and this is reproduced below.

Table 1. Patient Demographics Subdivided Into Patients With and Without Revision Surgery Post-ACI Treatment.

Patient Characteristics	Total Patients (*N* = 170)
Male–female	110:60
Age at ACI (years), mean ± SD [range]	37.3 ± 9.7 [15.1-65.8]
Follow-up time (years), mean ± SD [range]	10.9 ± 3.5 [4.6-18.6]
Age at follow-up (years), mean ± SD [range]	48.1 ± 10.2 [23.0-77.0]
Patients with single defects	124
Size of single defect (cm^2), median [IQR]	4.0 [2.4-6.0]
Anatomical location of single defect	
Medial femoral condyle	74
Lateral femoral condyle	28
Patella	10
Trochlea	8
Lateral tibial plateau	3
Medial tibial plateau	1
Patients with multiple defects	46
Previous operations [yes–no] (n)	151:12 (163)
Patients with co-incidental surgery [yes:no]	100:70

The authors kindly supplied KM plots with risk table and number of events (n=26). The failure definition was TKR. This was a more restricted definition of failure than that used by Nawaz et al and therefore superior success might be anticipated. However, since a main aim of intervention is delay or avoidance of TKR, this outcome definition might be considered more relevant to cost-effectiveness and the NHS.

The reconstructed KM plot for Dugard et al (2017) is shown in Figure 6 left together with the best parametric model (Gompertz) according to ranking of AIC plus BIC scores (Appendix 8.4). No models provided really good visual fits. Figure 6 right shows the extrapolation of six parametric models to 75 years. Of the models tested the Gompertz provides the most favourable failure profile. The least favourable model (exponential) predicts lifetime failure of approximately 70%.

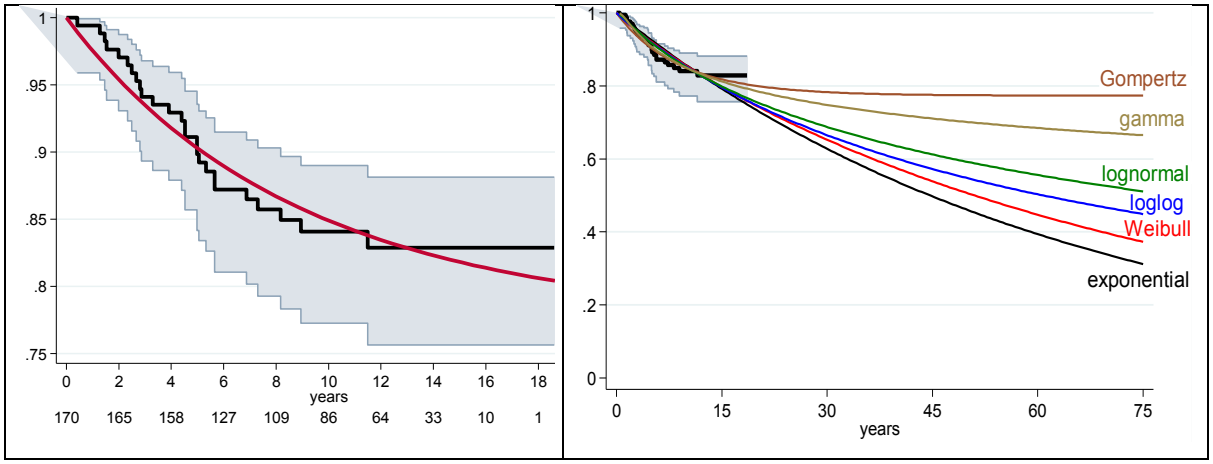


Figure 6: Dugard et al., 2017 KM plot and parametric models

[C] Implications for economic modelling

For the AG's original base-case the following treatment failure inputs were employed:

- MF failure − parametric model of reconstructed IPD pooled from Layton et al (2015)[42] (n = 3,498), Saris et al (2012)[46] (n = 61) and Knutsen et al (2007)[44] (n = 40)
- ACI failure − parametric model of reconstructed IPD for the whole cohort from Nawaz et al (2014)[3] (n = 827). In a sensitivity analysis the Nawaz et al, subgroup that had received no previous intervention (n = 547) was used.

Figure 7 (left) shows the impact on the parametric model for MF failure of substituting Knutsen et al (2016) IPD for Knutsen et al (2007); the two best fit models are shown. This indicates little change from the AG's original economic input and implies likely small impact on economic output. For comparison the MF failure model submitted in the Sobi economic model is also shown; this was based on the observation that at 5 years, 16.4% had failed in the TIG/ACT trial and fitting an exponential model to this observation. Figure 7 (right) shows the KM plot and two best fit models for MF failure when only Knutsen et al (2016) and Saris et al (2009) are pooled. The exponential fit is very similar to the Sobi model while the lognormal model suggests somewhat less failure. If Knutsen et al (2016) and Vanlauwe et al (2011)[25] are pooled the best fit is provided by a Gamma model and the predicted failure at 75 years is only 53%.

Best parametric fits to 3 pooled MF studies (Knutsen 2016, Saris 2009, Layton 2015)

Best parametric fits to 2 pooled MF studies (Knutsen 2016, and Saris 2009)

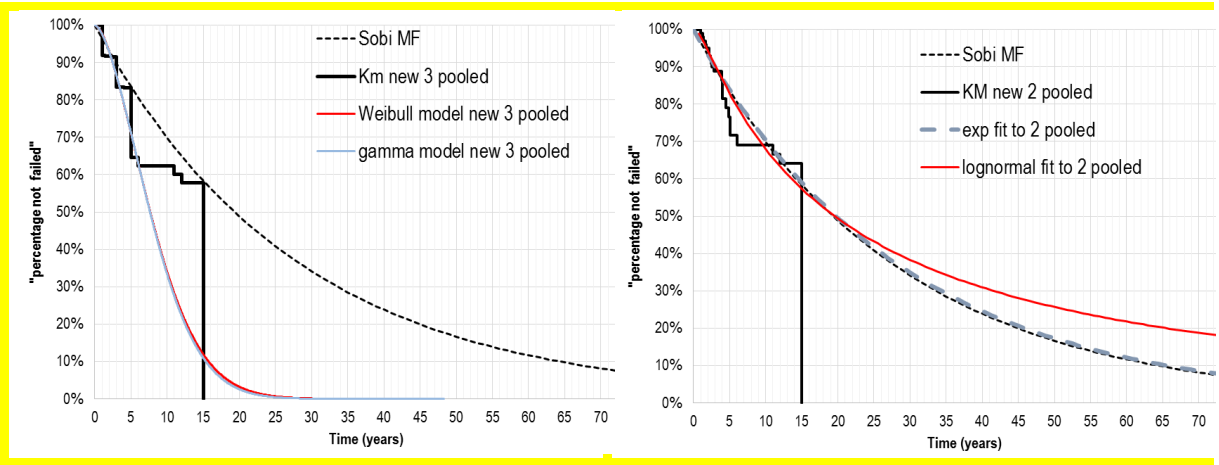


Figure 7: MF failure models based on pooling with Knutsen 2016 rather than Knutsen 2007 reconstructed IPD.

Figure 8 left shows the AG's base case and sensitivity analysis models of failure based on the Nawaz et al (20140 study compared with the Sobi KM (five pooled studies, but excluded Nawaz) and Sobi parametric model. Figure 8 right shows the Dugard KM plot for ACI failure (TKR) and the best model fit compared with the Sobi model.

Best parametric fits to Nawaz whole cohort and Nawaz no-previous subgroup Sobi KM and Gompertz model shown for comparison

KM and best parametric fit to Dugard 2017; Sobi Gompertz model shown for comparison

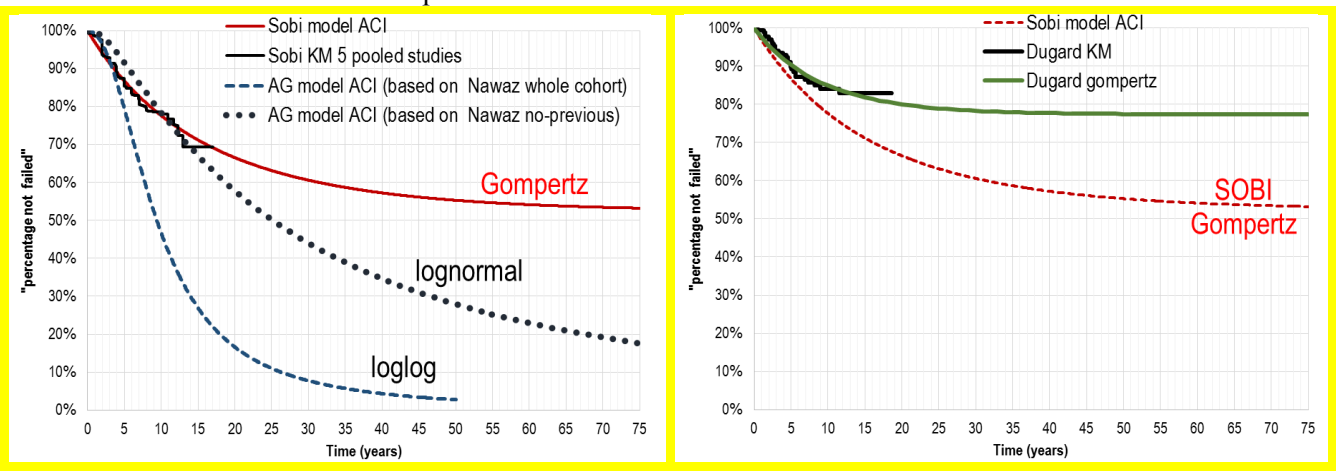


Figure 8: ACI failure models based on Nawaz et al. 2014 and Dugard et al. 2017 reconstructed IPD

6 DE NOVO ECONOMIC MODELLING

Reported below are the results of the additional economic analyses undertaken, incorporating new parameter values, in particular the survival curves for Knutsen et al (2016) paper.[5] Unless specified, the model structure and parameter values remain the same as those in the initial HTA report.[23] One difference from the first report is that NICE asked us to drop the MF (MF) scenario, in which is MF failed, patients could have a second MF.

6.1 Original base-case

Data used for ACI failure rates: Nawaz et al 2014 (whole cohort)[3]

Data used for MF failure rates: Pooled data (Layton et al 2015,[42] Knutsen et al 2007,[44] Saris et al 2009[46])

ACI cell costs: £16,000

Cost of harvesting: £870

Cost of implantation: £2,396

MF is nearly always done as a day case procedure

Table 2: Deterministic and probabilistic results for the original base-case analysis (Table 36 in HTA report)

Procedure	Total mean costs £	Total mean QALYs	Incremental costs £	Incremental QALYs	ICER versus MF(ACI)	Comparator
Deterministic - undiscounted						
MF (ACI)	7,736	34.2885	-	-	-	-
ACI (MF)	22,661	35.5596	14,926	1.2711	Extendedly dominated	MF(ACI)
ACI (ACI)	24,134	35.6999	1,473	0.1403	11,619	MF(ACI)
Deterministic – discounted						
MF (ACI)	6,248	17.1350	-	-	-	-
ACI (MF)	21,400	17.9304	15,152	0.7954	Extendedly dominated	MF(ACI)
ACI (ACI)	22,461	17.9953	1,062	0.0650	18,844	MF(ACI)
Probabilistic – discounted						
MF (ACI)	6,261	17.1523	-	-	-	-
ACI (MF)	21,410	17.9048	15,210	0.7525	Extendedly dominated	MF(ACI)
ACI (ACI)	22,532	17.9872	1,061	0.0824	19,487	MF(ACI)

Table 2 presents the results from the original base-case analysis which was presented in the HTA report.[23] The discounted deterministic results show that MF(ACI) was the least costly option and had the fewest QALYs; although ACI(ACI) generated the most QALYs, it was also the most expensive

option. The option of ACI(MF) was extendedly dominated by a linear combination of MF(ACI) and ACI(ACI), and therefore this option was eliminated from the comparison. The ICER comparing ACI(ACI) with MF(ACI) was just under £19,000; doing ACI first is more cost-effective. The discounted probabilistic results were very similar. Figure 9 shows the cost-effectiveness analysis for the two remaining options. The graph shows that, for amounts below £20,000, MF(ACI) is the most cost-effective option; at a willingness to pay of £20,000 there is not much difference between the two options, and, at a willingness to pay above £20,000, ACI(ACI) is probably more cost-effective.

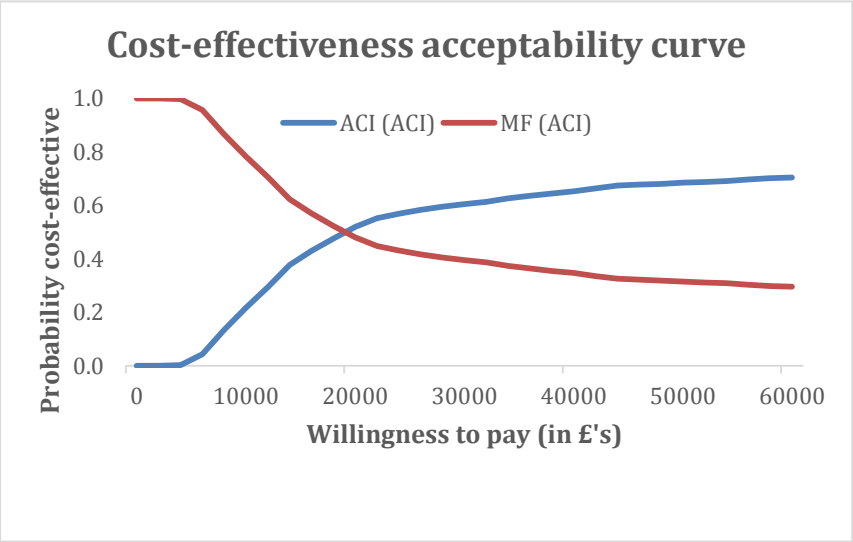


Figure 9: Cost-effectiveness acceptability curve (original base-case)

6.2 New analyses using the Knutsen et al (2016) paper – different piecewise models

Data used for ACI failure rates: Knutsen et al 2016[5]

Data used for MF failure rates: Knutsen et al 2016[5]

ACI cell costs: £16,000

Cost of harvesting: £870

Cost of implantation: £2,396

MF is nearly always done as a day case procedure

Table 3: Cost-effectiveness acceptability curve (original base-case)

Procedure	Total mean costs £	Total mean QALYs	Incremental costs £	Incremental QALYs	ICER versus MF(ACI)	Comparator
Deterministic – piecewise Gompertz for both ACI and MF						
MF (ACI)	5814	16.9029	-	-	-	-
ACI (MF)	21031	18.9563	15217	2.0534	7,411	MF (ACI)
ACI (ACI)	21604	18.6471	573	-0.3092	Dominated	ACI(MF)
Deterministic – piecewise Weibull for both ACI and MF						

MF (ACI)	5557	16.8256	-	-	-	-
ACI (MF)	21112	18.5123	15555	1.6867	9222	MF (ACI)
ACI (ACI)	21794	18.5511	682	0.0388	17597	ACI(MF)
Deterministic – piecewise Gompertz for ACI and piecewise Rayleigh for MF						
MF (ACI)	5739	16.8798	-	-	-	-
ACI (MF)	21002	18.6140	15263	1.7432	8801	MF (ACI)
ACI (ACI)	21604	18.6471	601	0.0331	18187	ACI(MF)

Table 3 presents the results using the Knutsen et al (2016)[5] paper and using different piecewise survival methods. The discounted deterministic results show that MF(ACI) was the least costly option and had the fewest QALYs. When using piecewise Gompertz for both for ACI and MF, ACI(ACI) was dominated by ACI(MF), and therefore this option was eliminated from the comparison. The ICER comparing ACI(MF) with MF(ACI) was just under £7,500.

When using either the piecewise Weibull for both ACI and MF or the piecewise Gompertz for ACI and piecewise Rayleigh for MF, the ICER comparing MF(ACI) with ACI(MF) was around £9,000 and the ICER comparing ACI(ACI) with ACI(MF) was around £18,000.

6.3 New analyses using the Knutsen et al (2016) paper – using the lognormal model

Data used for ACI failure rates: Knutsen et al 2016[5]

Data used for MF failure rates: Knutsen et al 2016[5]

ACI cell costs: £16,000

Cost of harvesting: £870

Cost of implantation: £2,396

MF is nearly always done as a day case procedure

Table 4: Deterministic and probabilistic results using a lognormal model

Procedure	Total mean costs £	Total mean QALYs	Incremental costs £	Incremental QALYs	ICER versus MF(ACI)	Comparator
Deterministic - undiscounted						
MF (ACI)	5943	33.2496	-	-	-	-
ACI (MF)	22209	36.7408	16265	3.4912	4659	MF (ACI)
ACI (ACI)	23346	36.8440	1138	0.1032	11021	ACI(MF)
Deterministic – discounted						
MF (ACI)	5059	16.6869	-	-	-	-
ACI (MF)	21222	18.4154	16164	1.7285	9351	MF (ACI)
ACI (ACI)	22032	18.4622	809	0.0468	17286	ACI(MF)
Probabilistic – discounted						
MF (ACI)	5078	16.7200	-	-	-	-
ACI (MF)	21234	18.4383	16155	1.7183	9402	MF (ACI)

ACI (ACI)	22038	18.4754	805	0.0371	21683	ACI(MF)

Table 4 presents the results using the Knutsen et al (2016)[5] paper and using the lognormal survival methods. The discounted deterministic results show that MF(ACI) was the least costly option and had the fewest QALYs; although ACI(ACI) generated the most QALYs, it was also the most expensive option. The ICER comparing MF(ACI) with ACI(MF) was around £9,000 and the ICER comparing ACI(ACI) with ACI(MF) was around £17,000. The discounted probabilistic results were similar.

6.4 Using data for ACI from Nawaz et al (2014) and pooled data from three studies for microfracture

Data used for ACI failure rates: Nawaz et al 2014[3]

1. whole cohort, 2. previous procedures, 3. no previous procedures

Data used for MF failure rates: Pooled data (Layton et al 2015,[42] Knutsen et al 2016,[5] Saris et al 2009[46])

ACI cell costs: £16,000

Cost of harvesting: £870

Cost of implantation: £2,396

MF is nearly always done as a day case procedure

Table 5: Deterministic and probabilistic results using Nawaz et al (2014) for ACI and pooled data from three studies for microfracture

Procedure	Total mean costs £	Total mean QALYs	Incremental costs £	Incremental QALYs	ICER versus MF(ACI)	Comparator
Deterministic discounted– Nawaz et al (whole cohort)						
MF (ACI)	6138	17.0573	-	-	-	-
ACI (MF)	21400	17.9304	15262	0.8731	Extendedly dominated	MF (ACI)
ACI (ACI)	22461	17.9953	1062	0.0650	17401	MF (ACI)
Probabilistic discounted– Nawaz et al (whole cohort)						
MF (ACI)	6159	17.0648	-	-	-	-
ACI (MF)	21540	17.9439	15381	0.8791	Extendedly dominated	MF (ACI)
ACI (ACI)	22611	18.0249	1072	1072	17137	MF (ACI)
Deterministic discounted– Nawaz et al (previous procedures)						
MF (ACI)	6138	17.0573	-	-	-	-
ACI (MF)	21462	17.4918	15324	0.4346	Extendedly dominated	MF (ACI)
ACI (ACI)	22746	17.5661	1284	0.0743	32636	MF (ACI)
Probabilistic discounted– Nawaz et al (previous procedures)						
MF (ACI)	6169	17.0754	-	-	-	-

ACI (MF)	21473	17.4844	15305	0.4091	Extendedly dominated	MF (ACI)
ACI (ACI)	22769	17.5768	1296	0.0924	33106	MF (ACI)
Deterministic discounted– Nawaz et al (no previous procedures)						
MF (ACI)	6138	17.0573	-	-	-	-
ACI (MF)	21101	18.7446	14963	1.6874	8868	MF (ACI)
ACI (ACI)	21644	18.7793	543	0.0347	15659	ACI(MF)
Probabilistic discounted– Nawaz et al (no previous procedures)						
MF (ACI)	6164	17.0564	-	-	-	-
ACI (MF)	21113	18.7514	14949	1.6950	8819	MF (ACI)
ACI (ACI)	21656	18.7952	544	0.0438	12421	ACI(MF)

When using data pooled for three studies for microfracture compared with using the Nawaz et al cohort for ACI (whole cohort or previous procedures or no previous procedures): MF(ACI) was the cheapest and also produced the fewest QALYs. As shown in Table 5, when using the whole Nawaz cohort or the Nawaz cohort with previous procedures: ACI(MF) was extendedly dominated by a linear combination of MF(ACI) and ACI(ACI), and therefore this option was eliminated from the comparison. The deterministic ICERs comparing ACI(ACI) with MF(ACI) was just over £17,000 when the whole Nawaz cohort was used for ACI; and the ICER was over £32,000 when using the Nawaz cohort who had previous procedures. For the Nawaz cohort with no previous procedures, the ICER comparing MF(ACI) with ACI(MF) was around £9,000 and the ICER comparing ACI(ACI) with ACI(MF) was around £16,000. Discounted probabilistic results were similar. The corresponding cost-effectiveness acceptability curves are shown in Figure 10.

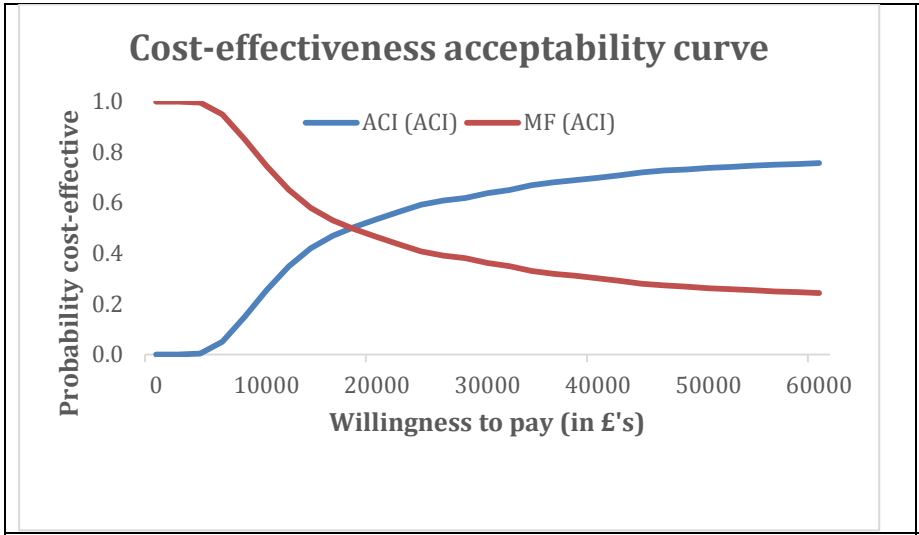


Figure 10a: Nawaz et al – whole cohort

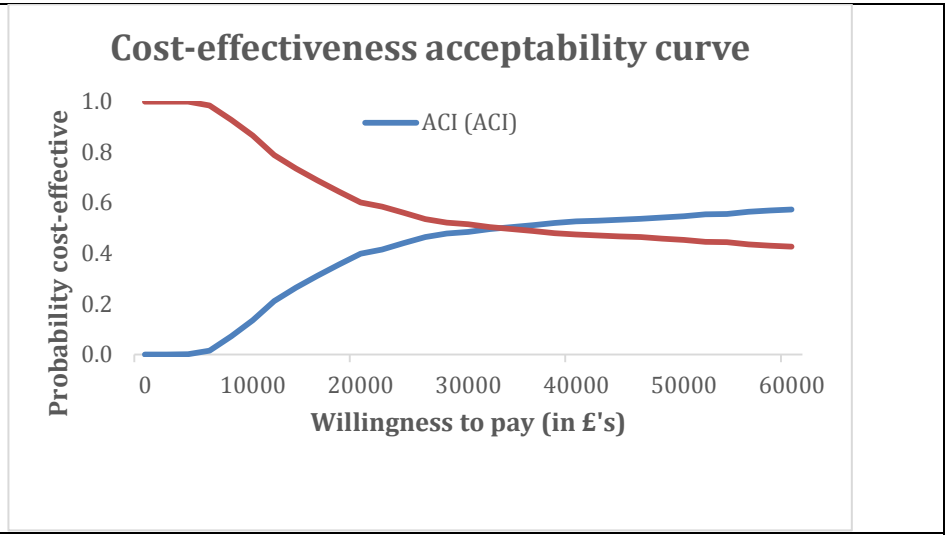


Figure 10b: Nawaz et al – previous procedures

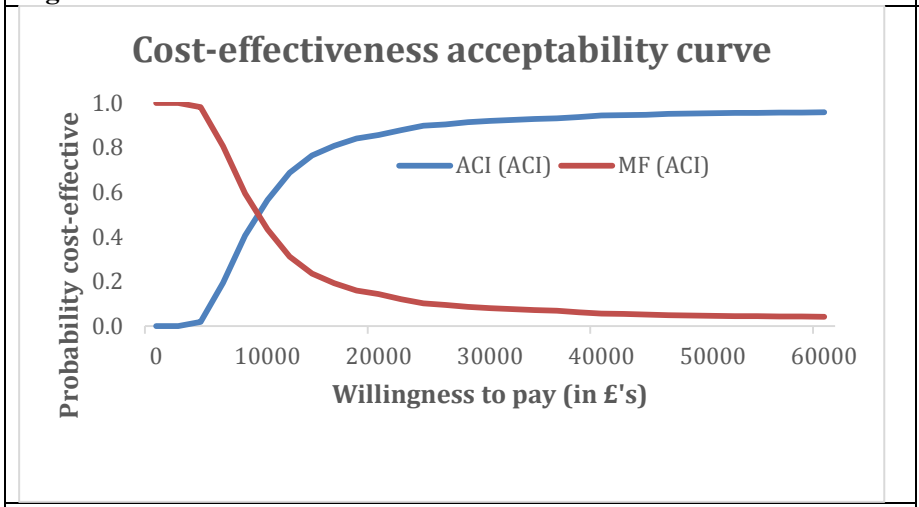


Figure 10c: Nawaz et al – no previous procedures

Figure 10: Cost-effectiveness acceptability curve - using data for ACI from Nawaz et al and pooled data from three studies for microfracture

6.5 Using data for ACI from Nawaz et al (2014) and pooled data from two studies for microfracture

In this analysis, we exclude the very large observational series from Layton et al from the USA, in which patients were much older on average (47 years) even after including only the commercial cover patients.

Data used for ACI failure rates: Nawaz et al 2014[3]

1. whole cohort, 2. previous procedures, 3. no previous procedures

Data used for MF failure rates: Pooled data (Knutsen et al 2016,[5] Saris et al 2009[46])

ACI cell costs: £16,000

Cost of harvesting: £870

Cost of implantation: £2,396

MF is nearly always done as a day case procedure

Table 6: Deterministic and probabilistic results using Nawaz et al (2014) for ACI and pooled data from two studies for microfracture

Procedure	Total mean costs £	Total mean QALYs	Incremental costs £	Incremental QALYs	ICER versus MF(ACI)	Comparator
Deterministic discounted– Nawaz et al (whole cohort)						
MF (ACI)	5406	16.7882	-	-	-	-
ACI (MF)	21400	17.9304	15993	1.1422	14002	MF (ACI)
ACI (ACI)	22461	17.9953	1062	0.0650	16345	ACI (MF)
Probabilistic discounted– Nawaz et al (whole cohort)						
MF (ACI)	5430	16.7785	-	-	-	-
ACI (MF)	21454	17.8940	16024	1.1156	Extendedly dominated	MF (ACI)
ACI (ACI)	22509	17.9958	1055	0.1017	14030	MF (ACI)
Deterministic discounted– Nawaz et al (previous procedures)						
MF (ACI)	5406	16.7882	-	-	-	-
ACI (MF)	21462	17.4918	16056	0.7036	Extendedly dominated	MF (ACI)
ACI (ACI)	22746	17.5661	1284	0.0743	22288	MF (ACI)
Probabilistic discounted– Nawaz et al (previous procedures)						
MF (ACI)	5413	16.7710	-	-	-	-
ACI (MF)	21284	17.4986	15871	0.7276	Extendedly dominated	MF (ACI)
ACI (ACI)	22583	17.6216	1298	0.1230	20186	MF (ACI)
Deterministic discounted– Nawaz et al (no previous procedures)						
MF (ACI)	5406	16.7882	-	-	-	-
ACI (MF)	21101	18.7446	15695	1.9565	8022	MF (ACI)
ACI (ACI)	21644	18.7793	543	0.0347	15659	ACI (MF)
Probabilistic discounted– Nawaz et al (no previous procedures)						

MF (ACI)	5408	16.8065	-	-	-	-
ACI (MF)	21028	18.7471	15620	1.9405	8049	MF (ACI)
ACI (ACI)	21576	18.7834	549	0.0363	15105	ACI (MF)

When using data pooled for two studies for microfracture compared with using the Nawaz et al cohort for ACI (whole cohort or previous procedures or no previous procedures): MF(ACI) was the cheapest and also produced the fewest QALYs. As shown in Table 6, when using the Nawaz cohort with previous procedures: ACI(MF) was extendedly dominated by a linear combination of MF(ACI) and ACI(ACI), and therefore this option was eliminated from the comparison. The deterministic ICER comparing ACI(ACI) with MF(ACI) was just over £22,000 when using the Nawaz cohort who had previous procedures. The deterministic results for the whole Nawaz cohort, the ICER comparing MF(ACI) with ACI(MF) was around £14,000 and the ICER comparing ACI(ACI) with ACI(MF) was around £16,000. For the Nawaz cohort with no previous procedures, the ICER comparing MF(ACI) with ACI(MF) was around £8,000 and the ICER comparing ACI(ACI) with ACI(MF) was around £15,500. Discounted probabilistic results were similar. The corresponding cost-effectiveness acceptability curves are shown in Figure 11.

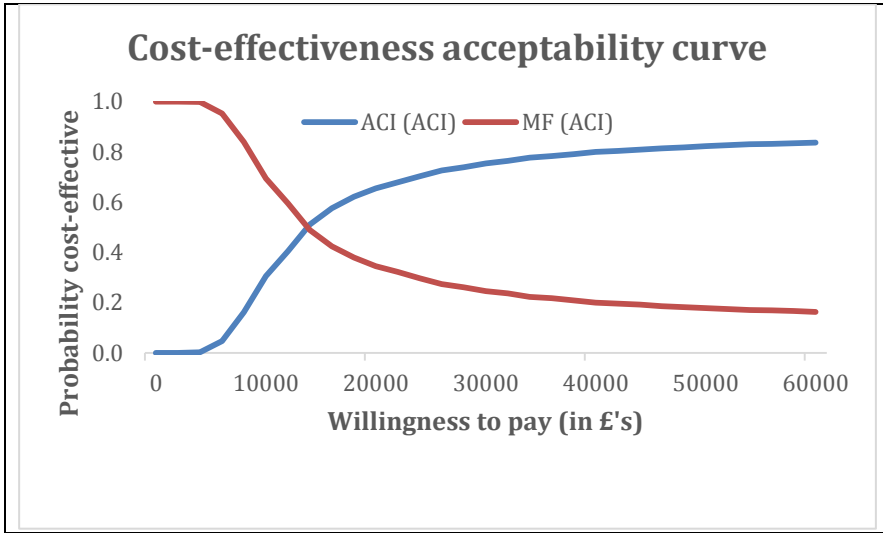


Figure 11a: Nawaz et al – whole cohort

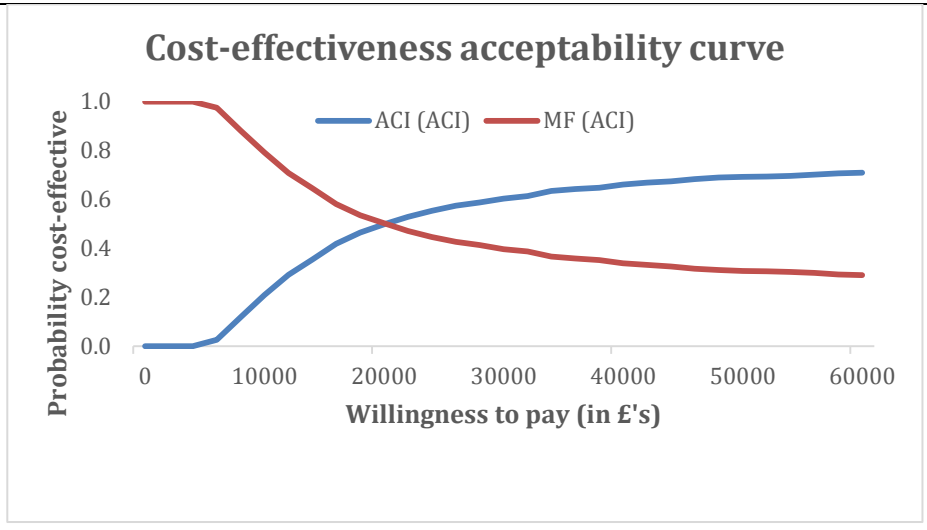


Figure 11b: Nawaz et al – previous procedures

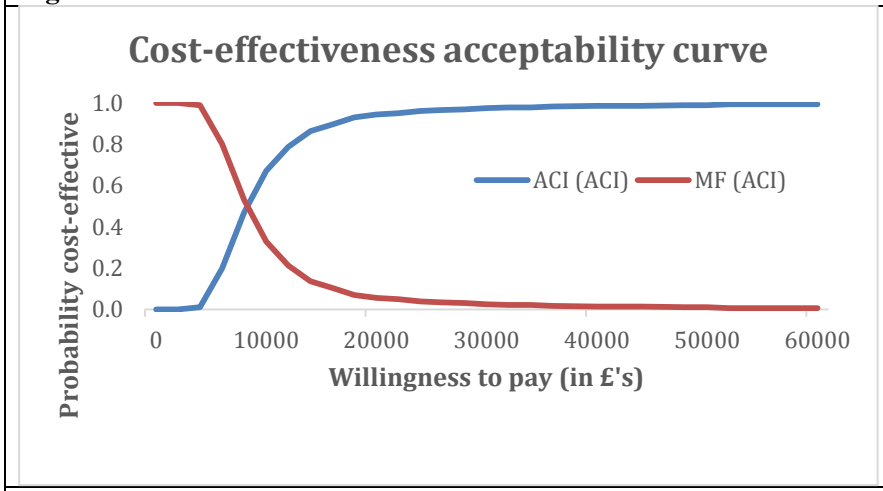


Figure 11c: Nawaz et al – no previous procedures

Figure 11: Cost-effectiveness acceptability curve - using data for ACI from Nawaz et al and pooled data from two studies for microfracture

6.6 Using data for ACI from Dugard et al (2017) and pooled data for microfracture

The Dugard study data comes from the RJAH Hospital in Oswestry, and comes from a study that aimed to develop a tool to predict which patients would do best after ACI. Data on 170 patients were used, and provide success rates, albeit from a single centre of excellence with 83% of operations done by one surgeon. This is the form of ACI which is referred to in the NICE scope as "traditional" ACI.

Data used for ACI failure rates: Dugard et al 2017[9]

Data used for MF failure rates:

- Pooled data (Layton et al 2015,[42] Knutsen et al 2016,[5] Saris et al 2009[46])
- Pooled data (Knutsen et al 2016,[5] Saris et al 2009[46])

ACI cell costs: £16,000

Cost of harvesting: £870

Cost of implantation: £2,396

MF is nearly always done as a day case procedure

Table 7: Deterministic and probabilistic results using Dugard et al (2017) for ACI and pooled data for microfracture

Procedure	Total mean costs £	Total mean QALYs	Incremental costs £	Incremental QALYs	ICER versus MF(ACI)	Comparator
Deterministic discounted – MF pooled data for three studies						
MF (ACI)	6138	17.0573	-	-	-	-
ACI (MF)	20840	19.1424	14702	2.0852	7050	MF (ACI)
ACI (ACI)	21158	19.1600	318	0.0175	18140	ACI (MF)
Probabilistic discounted– MF pooled data for three studies						
MF (ACI)	6145	17.0303	-	-	-	-
ACI (MF)	20954	19.1360	14808	2.1057	7032	MF (ACI)
ACI (ACI)	21273	19.1666	320	0.0306	10465	ACI (MF)
Deterministic discounted– MF pooled data for two studies						
MF (ACI)	5406	16.7882	-	-	-	-
ACI (MF)	20840	19.1424	15433	2.3543	6556	MF (ACI)
ACI (ACI)	21158	19.1600	318	0.0175	18140	ACI (MF)
Probabilistic discounted– MF pooled data for two studies						
MF (ACI)	5382	16.7720	-	-	-	-
ACI (MF)	20830	19.1366	15447	2.3647	6533	MF (ACI)

ACI (ACI)	21148	19.1584	318	0.0218	14598	ACI (MF)

When using data from Dugard et al for ACI and pooled data for microfracture (three studies or two studies): again MF(ACI) was the cheapest and also produced the fewest QALYs. When pooling all three MF studies, the deterministic ICER comparing MF(ACI) with ACI(MF) was around £7,000 and the ICER comparing ACI(ACI) with ACI(MF) was around £18,000. When pooling all two MF studies, the deterministic ICER comparing MF(ACI) with ACI(MF) was around £6,500 and the ICER comparing ACI(ACI) with ACI(MF) was around £18,000 (see Table 7). Discounted probabilistic results were similar. The corresponding cost-effectiveness acceptability curves are shown in Figure 12.

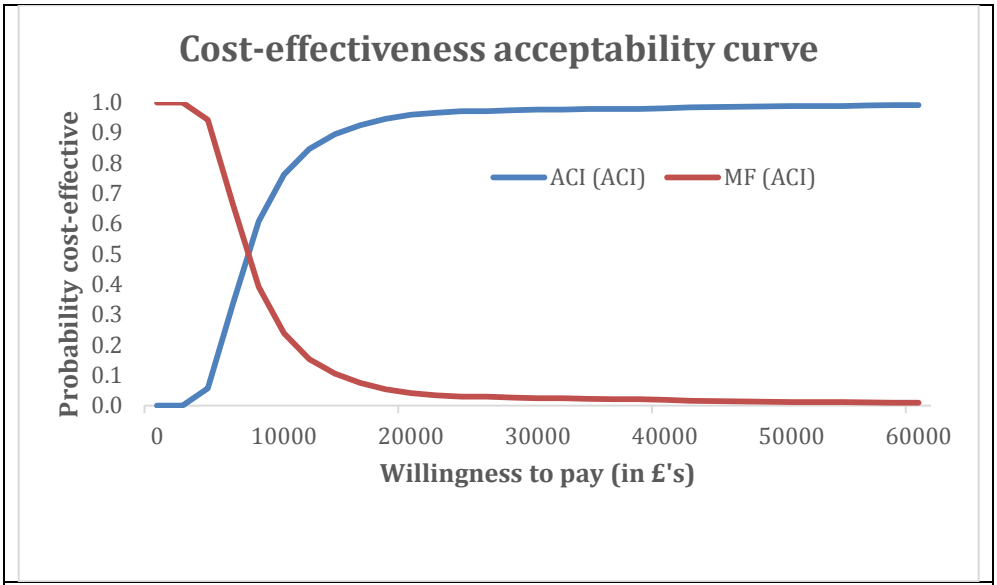


Figure 12a: MF pooled data for three studies

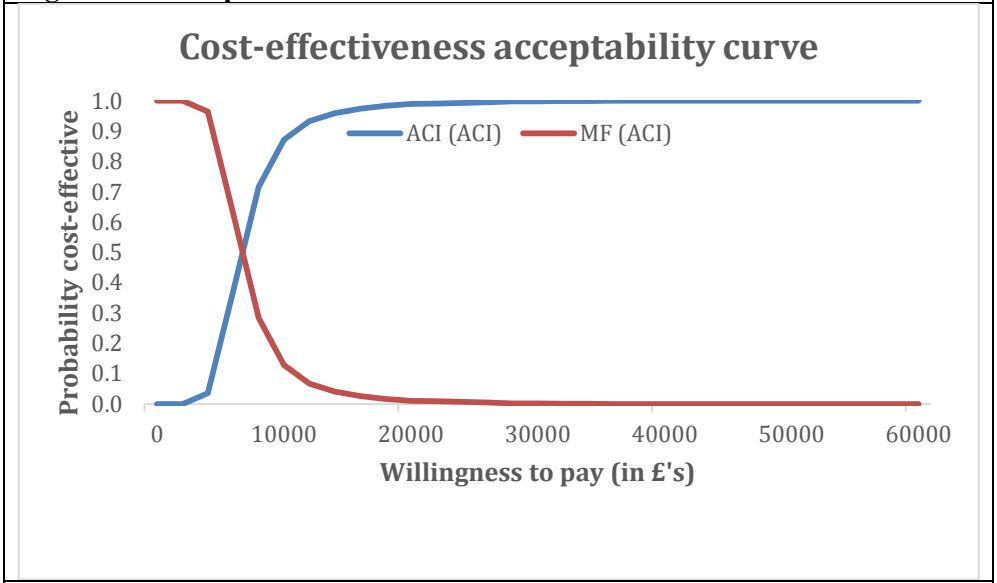


Figure 12b: MF pooled data for two studies

Figure 12: Cost-effectiveness acceptability curve - using data for ACI from Dugard et al and pooled data for microfracture

6.7 Assessment Group preferred base-case analysis - using data for ACI from Nawaz et al with no previous procedures (2014) and pooled data from two studies for microfracture

Data used for ACI failure rates: Nawaz et al 2014[3] - no previous procedures

Data used for MF failure rates: Pooled data (Knutsen et al 2016,[5] Saris et al 2009[46])

ACI cell costs: £16,000

Cost of harvesting: £870

Cost of implantation: £2,396

MF is nearly always done as a day case procedure

Table 8: AG preferred base-case analysis - deterministic and probabilistic results using Nawaz et al (2014) with no previous procedures for ACI and pooled data from two studies for microfracture

Procedure	Total mean costs £	Total mean QALYs	Incremental costs £	Incremental QALYs	ICER versus MF(ACI)	Comparator
Deterministic undiscounted– Nawaz et al (no previous procedures)						
MF (ACI)	6755	33.5525	-	-	-	-
ACI (MF)	21956	37.4216	15201	3.8691	3929	MF (ACI)
ACI (ACI)	22826	37.5038	870	0.0822	10586	ACI (MF)
Deterministic discounted– Nawaz et al (no previous procedures)						
MF (ACI)	5406	16.7882	-	-	-	-
ACI (MF)	21101	18.7446	15695	1.9565	8022	MF (ACI)
ACI (ACI)	21644	18.7793	543	0.0347	15659	ACI (MF)
Probabilistic discounted– Nawaz et al (no previous procedures)						
MF (ACI)	5408	16.8065	-	-	-	-
ACI (MF)	21028	18.7471	15620	1.9405	8049	MF (ACI)
ACI (ACI)	21576	18.7834	549	0.0363	15105	ACI (MF)

Data is replicated from Table 6 for ease. When using data pooled for two studies for microfracture compared with using the Nawaz et al cohort with no previous procedures: MF(ACI) was the cheapest and also produced the fewest QALYs. As shown in Table 8, for the Nawaz cohort with no previous procedures, the deterministic ICER comparing MF(ACI) with ACI(MF) was around £8,000 and the ICER comparing ACI(ACI) with ACI(MF) was around £15,500. Discounted probabilistic results were similar.

6.8 Assessment Group preferred base-case analysis – sensitivity analyses on prices

Data used for ACI failure rates: Nawaz et al 2014[3] - no previous procedures

Data used for MF failure rates: Pooled data (Knutsen et al 2016,[5] Saris et al 2009[46])

Cost of harvesting: £870

Cost of implantation: £2,396

MF is nearly always done as a day case procedure

Table 9: AG preferred base-case analysis - deterministic and probabilistic results using Nawaz et al (2014) with no previous procedures for ACI and pooled data from two studies for microfracture

Procedure	Total mean costs £	Total mean QALYs	Incremental costs £	Incremental QALYs	ICER versus MF(ACI)	Comparator
Deterministic discounted– cell price £8000						
MF (ACI)	5028	16.7882	-	-	-	-
ACI (MF)	13101	18.7446	8073	1.9565	4126	MF (ACI)
ACI (ACI)	13382	18.7793	281	0.0347	8091	ACI (MF)
Probabilistic discounted– cell price £8000						
MF (ACI)	5040	16.7569	-	-	-	-
ACI (MF)	13101	18.7399	8061	1.9830	4065	MF (ACI)
ACI (ACI)	13382	18.8053	281	0.0654	4294	ACI (MF)
Deterministic discounted– cell price £12000						
MF (ACI)	5217	16.7882	-	-	-	-
ACI (MF)	17101	18.7446	11884	1.9565	6074	MF (ACI)
ACI (ACI)	17513	18.7793	412	0.0347	11875	ACI (MF)
Probabilistic discounted– cell price £12000						
MF (ACI)	5231	16.7628	-	-	-	-
ACI (MF)	17113	18.7288	11882	1.9659	6044	MF (ACI)
ACI (ACI)	17531	18.7893	419	0.0606	6911	ACI (MF)

We are aware that confidential discounts are provided to the NHS by manufacturers, so in this sensitivity analysis we have reduced the costs of cells from £16,000 to £8,000 and £12,000. Table 9 shows when using the AG preferred base and reducing the cost of cells from £16,000 as in the base-case to £8,000, the deterministic ICER comparing MF(ACI) with ACI(MF) was around £4,000 and the ICER comparing ACI(ACI) with ACI(MF) was around £8,000. Also, when using the AG preferred base and reducing the cost of cells to £12,000, the deterministic ICER comparing MF(ACI) with ACI(MF) was around £6,000 and the ICER comparing ACI(ACI) with ACI(MF) was around £12,000. For both prices, the discounted probabilistic results were similar when comparing ACI(MF) with MF(ACI); however, the discounted probabilistic results were not as similar when comparing ACI(MF) with ACI(ACI) this was due to the incremental QALYs being near zero and hence the fluctuation in the ICER values. The corresponding cost-effectiveness acceptability curves are shown in Figure 13.

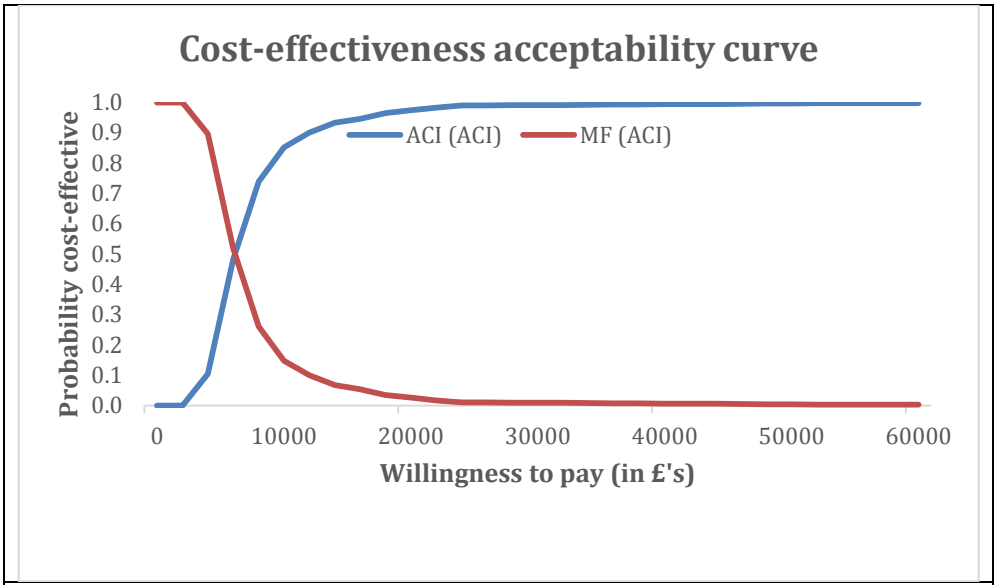


Figure 13a: Cell price £8,000

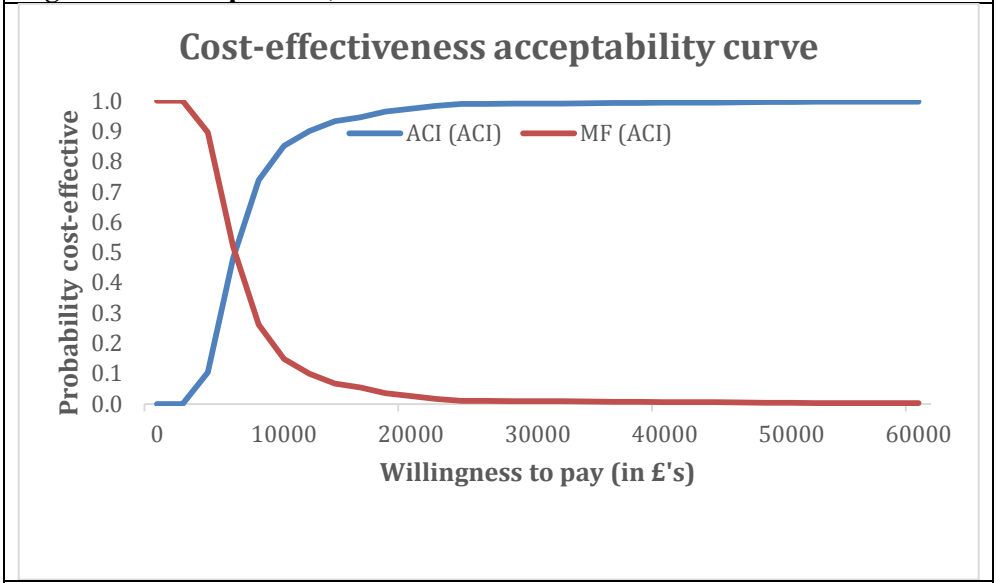


Figure 13b: Cell price £12,000

Figure 13: Cost-effectiveness acceptability curve - sensitivity analyses on prices

7 DISCUSSION

In the Summary in our previous report (now published as an HTA monograph), we said: *"There were more long-term studies of ACI than of MF. Using longer-term data than were available in the trials, microfracture comes out much less well. However, there are few long-term studies of MF, and extrapolation beyond observed data is subject to uncertainties".*

We produced a large number of survival curves based on extrapolation from studies with durations up to 5 years, and selected those which seemed most plausible, taking into account clinical opinion and the few long-term studies of microfracture. We took note of editorials such as that by Bert (2015)[49] who said: *"There is simply no justification in the literature to support the use of marrow stimulation procedures, especially MF, at this time."*

Our assumption was that microfracture would give good results for a few years, but would then progressively fail.

The Knutsen et al (2016) paper suggests that this assumption was wrong. The MF results in that study are about the best ever seen. What we cannot predict from the Knutsen MF data is what happens next. At 15 years follow-up their mean age is about 46 – too young to receive knee replacement. It is possible that the plateau in the Knutsen KM graph conceals failures managed on analgesics while waiting to age into the TKR range. The Layton et al (2015) data shows that many patients are on strong analgesics in the years after MF, which suggests that MF has not relieved symptoms.

One interpretation of the Knutsen MF data is that it provides success in the early years, but with some early failures (defined as needing re-operation), followed by a plateau (possibly including failures not receiving surgery) during which OA is developing, then followed by the start of knee replacement. It is possible that as the osteoarthritic cohort ages over the knee replacement threshold, the rate of TKR may increase. If so, fitting a curve based on the graph to 15 years might over-estimate benefit.

Other recent papers such as by Solheim et al (2016), give a more pessimistic account of microfracture, and the return to sport data show better results after ACI. However, even if we accept the Knutsen MF data, ACI still has some ICERs in the usually acceptable range.

As requested by NICE, we used an ACI implantation cost of £2,396 which assumes an overnight stay. The advice we have from clinical experts familiar with MACI is that it can be done on a day case basis but that overnight stays are common, partly because ACI was being done after tertiary referral to specialist centres.

Future research needs

The small study by Mumme et al (2016), on using nasal chondrocytes for autologous cartilage implantation needs to be repeated with larger numbers and longer follow-up. This is not really "fourth generation" ACI because it involves implanting not chondrocytes, but cartilage containing chondrocytes, grown in the laboratory. This will presumably be easier to implant because it can be cut to shape. And because the cartilage has already grown, rehabilitation time might be shorter. Hence, further trials are needed.

Conclusion

We have reviewed new evidence, which gives mixed messages. The 15 year data from one of the landmark trials, by Knutsen and colleagues (2016) challenges our previous assumption that most MF fails over time. However, the Solheim et al (2016) study suggests a higher MF failure rate.

We will never have an RCT in which patients are randomised to ACI or MF and followed for 20-30 years to see how many require TKR. And if we did, the results would be obsolete because the technology would have moved on. So decisions have to be made on the imperfect evidence that we currently have.

8 APPENDICES

8.1 Appendix A: New studies not used

Basad E, Wissing FR, Fehrenbach P, Rickert M, Steinmeyer J, Ishaque B. Matrix‐induced autologous chondrocyte implantation (MACI) in the knee: clinical outcomes and challenges. Knee Surg Sports Traumatol Arthrosc 2015;23:3729–3735. *Case series but only 25 with 5-year follow-up*

Devitt BM, Bell SW, Webster KE, Feller JA, Whitehead TS. Surgical treatments of cartilage defects of the knee: Systematic review of randomised controlled trials. Online The Knee; 2017.

DiBartola AC, Wright BM, Magnussen RA, Flanigan DC. Clinical Outcomes After Autologous Chondrocyte Implantation in Adolescents' Knees: A Systematic Review. Arthroscopy: The Journal of Arthroscopic and Related Surgery 2016;32:1905-1916. *Adolescent study but ACI-P*

Erggelet C, Vavken P. Microfracture for the treatment of cartilage defects in the knee joint – A golden standard? Journal of Clinical Orthopaedics and Trauma 2016;7:145–152. *Good review but nil of note new.*

Gille J, Peter Behrens P, Schulz AP, Oheim R, Kienast B.3 Matrix-Associated Autologous Chondrocyte Implantation: A Clinical Follow-Up at 15 Years. Cartilage 2016;7(4): 309–315. *Only 18 patients at follow-up*

Gobbi A, Whyte GP.One-Stage Cartilage Repair Using a Hyaluronic Acid–Based Scaffold With Activated Bone Marrow–Derived Mesenchymal Stem Cells Compared With Microfracture Five-Year Follow-up. The American Journal of Sports Medicine, 2016;44, No. 11 DOI: 10.1177/0363546516656179. *Comparison in non-randomised study, with patient allocation determined by what insurers would fund, with other differences between groups.*

Kraeutler MJ, Belk JW, Purcell JM, McCarty EC. Microfracture Versus Autologous Chondrocyte Implantation for Articular Cartilage Lesions in the Knee: A Systematic Review of 5-Year Outcomes. The American Journal of Sports Medicine. DOI: 10.1177/0363546517701912. *No new evidence*

Manco A, Goderecci R, Rughetti A, De Giogi A, Necozione S, Bernardi A, et al. Microfracture *versus* microfracture and platelet-rich plasma: arthroscopic treatment of knee chondral lesions. A two-year follow-up study. Joints 2016;4(3):142-147. *Enhanced version of MF but only 2-year follow-up*

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8.2 Appendix B: Knutsen et al (2016) – Table 1 reproduced

Knutsen et al (2016) Table 1 lists the year and type of failure for 17 and 13 failures of ACI and MF patients, respectively. The table is reproduced below.

Knutsen Table 1 copyright protected

TABLE I Data on the Patients Who Had Treatment Failure*

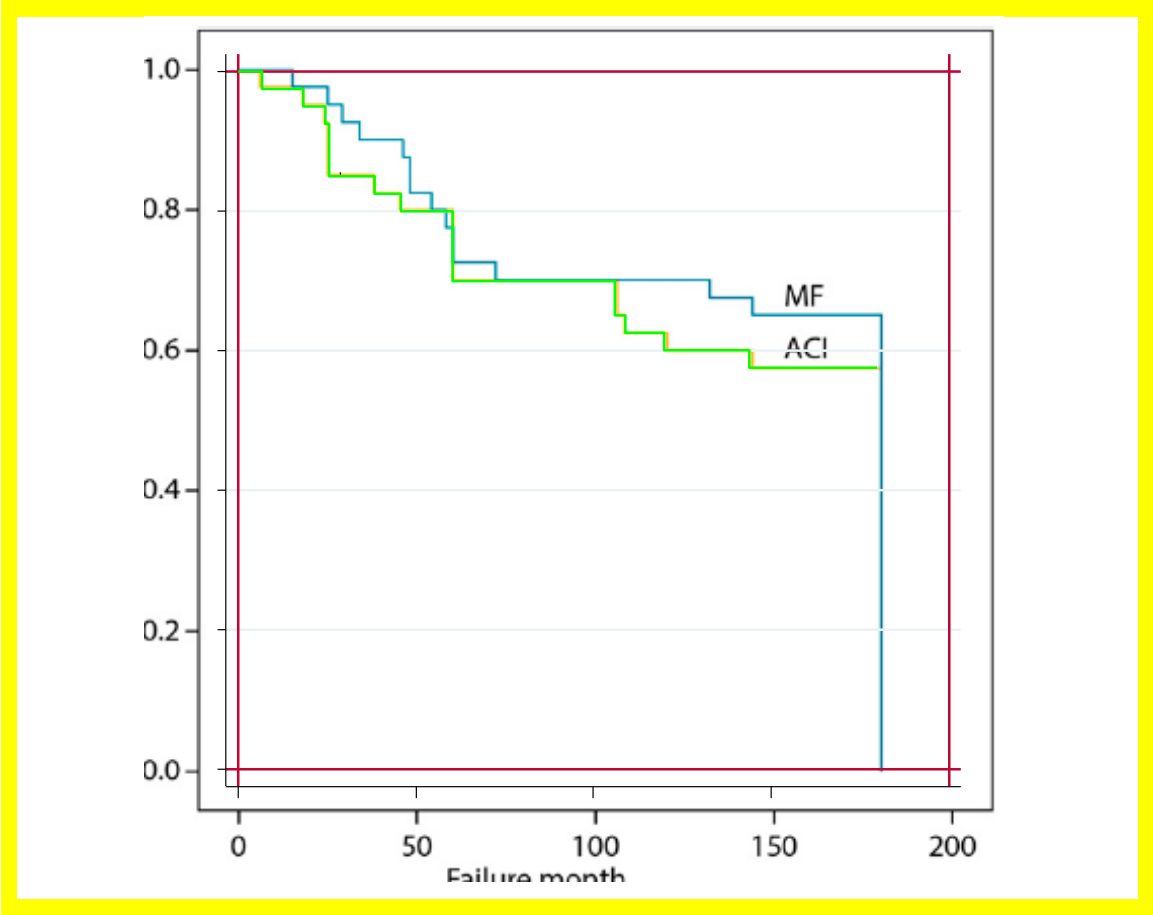
Case	Subsequent Procedure (Year)	VAS Pain Score	Lysholm Score
ACI			
1	HTO (2009)	52	52
2	TKR (2014)	30	78
3	Microfracture (2001)	65	54
4	Microfracture (2005)	60	60
5	TKR (2005)	25	68
6	Mosaicplasty (2005)	48	62
7	Mosaicplasty (2002), TKR (2010), revision (2010)	30	70
8	HTO (2002)	50	90
9	HTO (2013)	66	42
10	Microfracture (2002)	79	35
11	TKR (2012)	19	92
12	Microfracture (2002)	25	76
13	TKR (2009), revision (2011)	7	46
14	TKR (2008)	48	71
15	Microfracture (2004)	56	74
16	HTO and microfracture (2008)	68	79
17	Microfracture (2001)	5	86
Microfracture			
1	Repeat microfracture (2003)	55	57
2	Repeat microfracture (2003)	50	56
3	HTO (2011)	70	31
4	Mosaicplasty (2001)	0	100
5	TKR (2006)	10	92
6	TKR (2012)	37	50
7	HTO (2005)	50	55
8	HTO (2006)	20	91
9	HTO (2005)	49	43
10	Repeat microfracture (2003)	30	74
11	Repeat microfracture (2001)	5	86
12	ACI (2004)	20	90
13	TKR (2004), revision (2012)	70	50

*VAS = visual analog scale, ACI = autologous chondrocyte implantation, HTO = high tibial osteotomy, and TKR = total knee replacement.

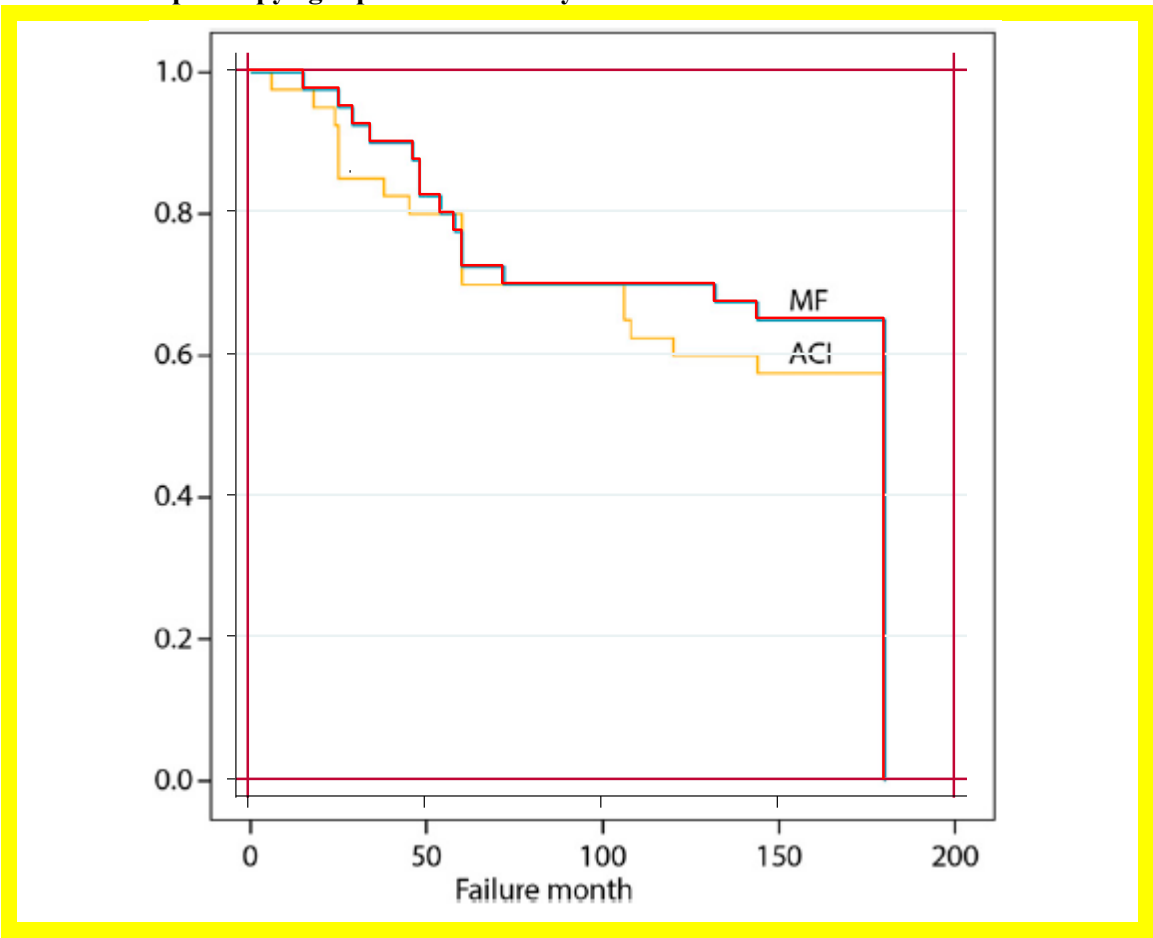
8.3 Appendix C: Comparison of reconstructed and published KM plots

The AG reconstructed individual patient data using the method of Guyot et al (2012). Reconstructed IPD-derived KM plots were overlaid on the published plots to test validity of reconstruction; these are shown below. The first figure shows the AG ACI plot overlaid the published plot (lime green on orange) and the second figure shows the AG MF plot overlaid the published MF plot (red on blue).

Knutsen KM plot copyright protected, overlayed with AG reconstruction



Knutsen KM plot copyright protected overlayed with AG reconstruction



8.4 Appendix D: Information criteria for parametric models

Knutsen et al (2016): parametric models using all KM data

Model ACI all	Obs	df	AIC	BIC
gamma	40	3	99.16426	104.2309
exponential	40	1	99.70127	101.3901
weibull	40	2	101.3015	104.6792
gompertz	40	2	99.16616	102.5439
lognormal	40	2	98.79929	102.1771
loglogistic	40	2	100.1045	103.4823
flexible	40	3	99.01643	104.0831
Model MF all	Obs		AIC	BIC
gamma	40	3	86.00548	91.07212
exponential	40	1	88.82858	90.51746
weibull	40	2	90.81149	94.18925
gompertz	40	2	89.62499	93.00274
lognormal	40	2	88.16659	91.54434
loglogistic	40	2	89.78233	93.16009
flexible	40	3	85.13576	90.2024

Knutsen (2016): parametric models using piecewise data

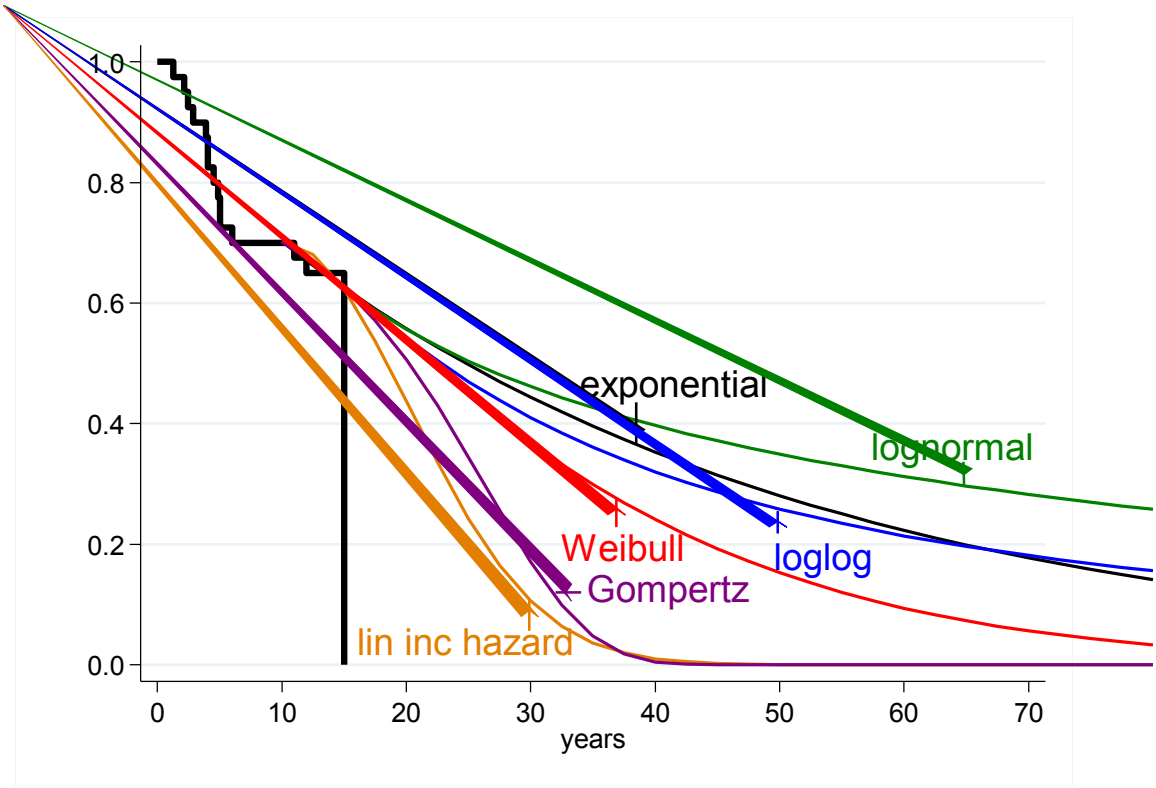
ACI phase one				
Model	Obs	df	AIC	BIC
gamma	40	3	63.43631	68.50295
exponential	40	1	66.79847	68.48735
weibull	40	2	61.46057	64.83833
gompertz	40	2	62.27524	65.653
lognormal	40	2	61.57564	64.9534
loglogistic	40	2	61.50365	64.88141
lin inc haz	40	1	59.68444	61.37332
ACI phase 2				
Model	Obs	df	AIC	BIC
exponential	29	1	48.54419	49.91149
weibull	29	2	47.45197	50.18656
gompertz	29	2	44.58915	47.32374
lognormal	29	2	46.60829	49.34289
loglogistic	29	2	47.26636	50.00095
lin inc haz	29	1	62.23092	63.59822
MF phase 1				
Model	Obs	df	AIC	BIC
gamma	40	3	68.46307	73.52971
exponential	40	1	67.50557	69.19445
weibull	40	2	66.70159	70.07935
gompertz	40	2	66.67456	70.05232
lognormal	40	2	67.14417	70.52193
loglogistic	40	2	66.92513	70.30289
lin inc haz	40	1	65.20457	66.89344
MF Phase 2				

Model	Obs	df	AIC	BIC
gamma	28	3	36.56007	40.55668
exponential	28	1	25.21227	26.54448
weibull	28	2	26.76022	29.42463
gompertz	28	2	26.90356	29.56797
lognormal	28	2	26.59395	29.25836
loglogistic	28	2	26.75921	29.42362
lin inc haz	28	1	25.03933	26.37154

Dugard et al (2017)

				rank	**rank**	**sum**		**AIC BIC**	**rank**	
model	**df**	**AIC**	**BIC**	**AIC**	**BIC**	**ranks**	**order**	**sum**	**sum**	**order**
gamma	3	201.4167	210.824	1	4	*5*	b	412.2407	4	d
exponential	1	203.8281	206.9639	4	1	*5*	b	410.792	2	b
weibull	2	205.5812	211.8528	6	6	12	e	417.434	6	f
gompertz	2	202.224	208.4956	2	2	4	a	410.7196	1	a
lognormal	2	202.2746	208.5462	3	3	*6*	c	410.8208	3	c
loglogistic	2	204.7815	211.0531	5	5	10	d	415.8346	5	e

8.5 Appendix E: Piecewise modelling of MF with the phase 3 start time set to 10 years



8.6 Appendix F: Network meta-analysis

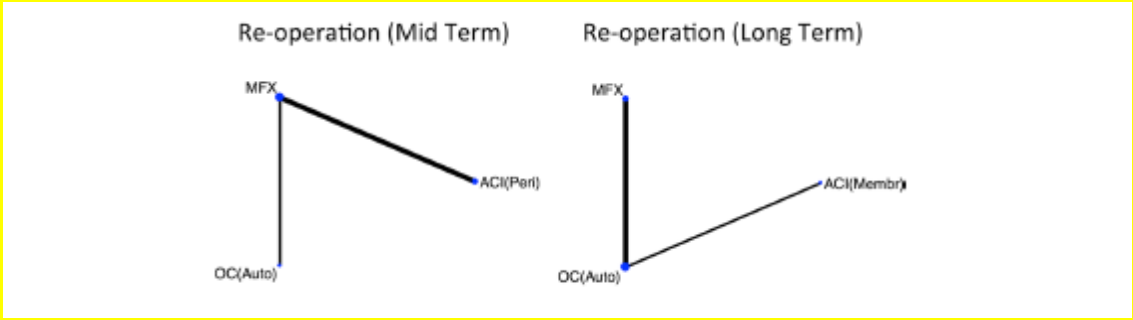
Riboh et al (2016) network meta-analysis (NMA) of knee cartilage repair interventions

Riboh et al (2016)[48] published a NMA for outcomes from RCTs comparing ACI, MF, and OAT (mosaicplasty). This meta-analysis was undertaken before the Knutsen et al (2016) paper became available. Seven outcomes were examined: short-term, mid-term and long-term failure rates (using odds ratios), Tegner and Lysholm scores, presence of hyaline cartilage on postoperative biopsy and graft hypertrophy. The analyses distinguished between different forms of ACI and MF interventions: ACI using collagen membrane (ACI-C); ACI using periosteal flap (ACI-P), and Matrix ACI (MACI); microfracture (MF) and augmented microfracture (AUG MF). Cumulative treatment rankings by Surface under the Cumulative Ranking (SUCRA) statistics were calculated so that ranking the interventions across all outcomes could be undertaken. The result from this analysis ranked the interventions in the following order: ACI-C, OAT, MACI, AUG MF, ACI-P, MF.

The ranking order of interventions by long-term failure rates was: ACI-C, OAT, MF. The authors' confidence in this ranking was low. With regards to failure rates the author's concluded: *"Clinical failure of cartilage repair, as defined by a re-operation on the same knee, is a critical measure of treatment efficacy. At 2-year follow up, there were no significant differences in re-operation rates between any of the treatment options. However, at 5- and 10-year follow-up, microfracture was the worst of all investigated treatments"*.

Because Riboh et al (2016) subdivided the ACI and MF interventions into several sub-types the networks for mid-term and long-term failure rates did not form closed loops and therefore tests for statistical inconsistency could not be undertaken. The Riboh networks for mid-term and long-term failure are shown below. Publications included in the long term network were: Ulstein et al (2014)[50], Gudas et al (2012)[51], Bentley et al (2012)[29]; for the mid-term network the publications were: Knutsen et al (2007)[44], Vanlauwe et al (2011)[25] and Gudas et al (2005).[52]

copyright protected



Riboh et al (2016) networks for mid-term and long term failure

The AG's remit was to consider the comparison ACI versus MF without distinction of intervention subtypes. The AG therefore re-examined mid-term and long-term failure using odds ratios as in Riboh but without distinguishing between intervention sub-types and including the newly available data from Knutsen et al (2016). This allowed generation of closed network loops (Figure 14) and tests for inconsistency.

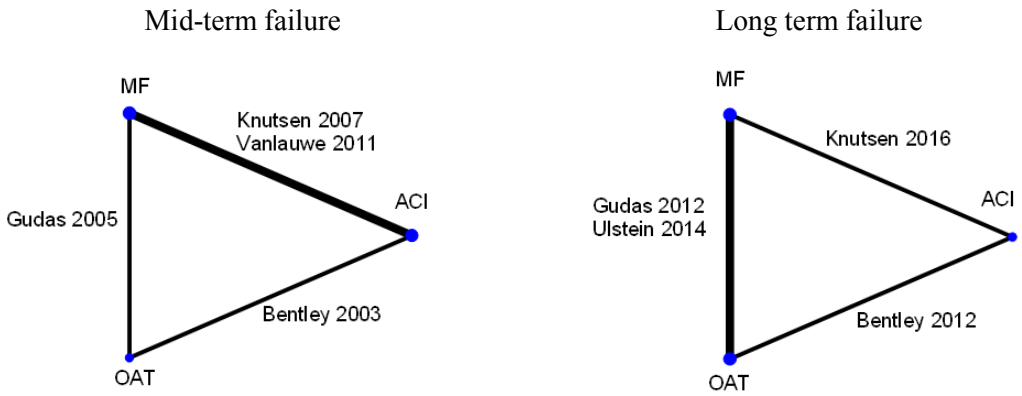


Figure 14: Network of studies for mid-term and long-term failure

The odds ratios for the mid-term and long-term failure networks are summarised in

Table 10 and Table 11; the corresponding direct comparison forest plots (random effects) are shown in Figure 15.

Table 10: Odds ratios in studies forming a network for mid-term failure

study	T1	T2	OR	lnOR	SElnOR
Vanlauwe_2011	ACI	MF	0.811364	-0.20904	0.534034
Knutsen_2007	ACI	MF	1	0	0.53548
Bentley_2003	ACI	OAT	0.719298	-0.32948	1.428963
Gudas_2005	MF	OAT	12.15	2.497329	1.0946

Table 11: Odds ratios in studies forming a network for long-term failure

study	T1	T2	OR	lnOR	SElnOR
Bentley_2012	OAT	AIC	5.810526	1.759671	0.465772
Gudas_2012	OAT	MF	0.272727	-1.29928	0.661915
Ulstein_2014	OAT	MF	0.462963	-0.77011	0.823273
Knutsen_2016	MF	ACI	0.703529	-0.35165	0.468215

For mid-term failure there appears to be some inconsistency, in that OAT is superior to MF and ACI is about equivalent to OAT, and therefore, one might expect ACI to be superior to MF; however, two RCTs with little evidence of statistical heterogeneity indicate ACI and MF are equivalent. In a design-by-treatment interaction model the p-value was 0.139 and in side splitting model, p-values for each comparison were also 0.139. These results may be due to lack of power in the tests rather than a lack of inconsistency.

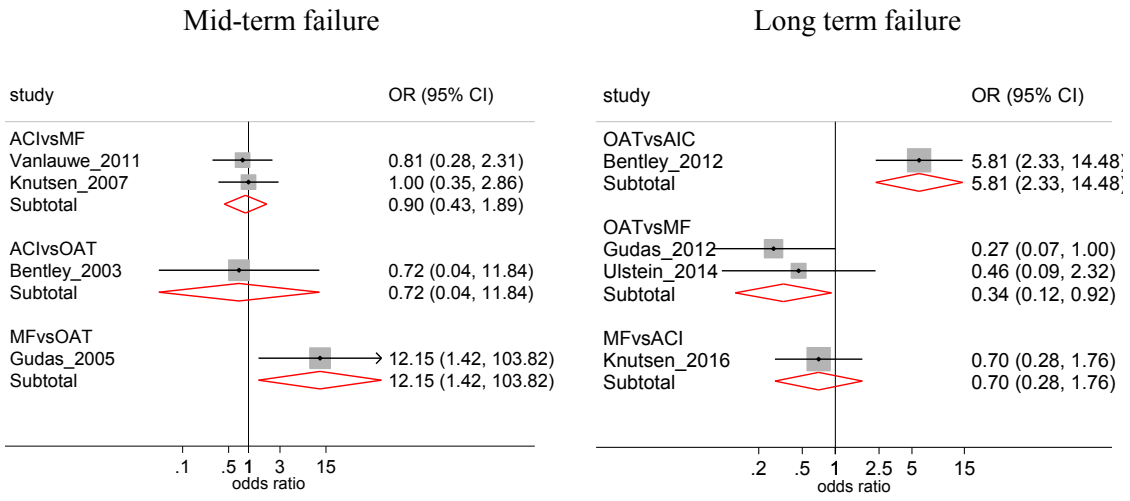


Figure 15: Forest plots of Odds Ratio for failure in the mid- and long-term

There are obvious signs of inconsistency in the long-term failure network in that on the basis that AIC is superior OAT and OAT is superior to MF one would expect that ACI would be very superior to MF, whereas the Knutsen et al (2016) study (MF vs ACI) indicates slight advantage

for MF. Given the very likely inconsistency between direct and indirect evidence design-by-treatment interaction model and the side splitting tests were undertaken. For the design-by-treatment interaction model a p-value (<0.0001) was obtained. The side splitting test results are summarised in Table 12. These tests indicate strong evidence of inconsistency in the network.

Table 12: Results of side splitting test for long-term failure

Side	Direct coefficient (SE)	Direct coefficient (SE)	Difference (SE)	P
ACI OAT	1.7597 (0.4658)	-1.4432 (0.6967)	3.2028 (0.8380)	<0.001
ACI MF	-0.3516 (0.4682)	2.8509 (0.6950)	-3.2026 (0.8380)	<0.001
MF OAT	-1.0915 (0.5159)	2.1113 (0.6604)	-3.2028 (0.8380)	<0.001

There are many potential reasons for the inconsistency seen, including: i] Bias in one or more of the studies in the NMA; ii] Differences between surgeons in their expertise in one or more of the interventions; iii] Differences between studies in the distribution of influential patient level treatment modifiers; iv] Differences in the interventions (e.g. the type of ACI employed in the studies); v] Differences between study centres in the application of post-surgery rehabilitation programmes; vi] Different decision making between surgeons and patients about undertaking a second surgical intervention; and vii] Differences in types, duration and sizes of lesions may be most important.

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Warwick Evidence Assessment group response to comments from consultees. 15th June.

On 7th June, we were given access to six documents received from consultees and others. Some of the comments refer to our March 2016 report, but one refers to our addendum of 30th May 2017. For clarity, we will refer to the Warwick reports as follow;

- Warwick assessment report March 2105 – WAR 1
- Additional analyses requested by NICE and delivered in March 2016 – WAR 2.
- Addendum May 2017 – WAR 3.

BASK comments, submitted 25th February 2017.

This response was to WAR2. We have no comments on the BASK document. It was written on behalf of BASK by Leela Biant, who was one of our expert advisers and attended the first appraisal committee meeting, in 2015, before she took on her current role in BASK.

Oswestry comments.

These are dated 28th March 2017 and also refer to WAR2. It is useful that recent ACTIVE analyses support our use of the Nawaz data for long-term results. ACTIVE was a trial, but by using a large number of NHS centres, the results may be closer to results in routine NHS care.

Two factors should be noted when considering the ACTIVE results. Firstly, around a third of recruits had had previous repair attempts such as microfracture and drilling. NB we exclude debridement from the category of "previous repairs". Debridement may improve symptoms for example by removing loose bits of cartilage, but it cannot repair the cartilage defect. However it does not damage the underlying bone so does not reduce the effectiveness of subsequent ACI. The term used by Vericel is useful for describing previous procedures that reduce the effectiveness of ACI: "previous surgical interventions violating the subchondral bone".

Oswestry point 3. We therefore disagree with the Oswestry term "secondary repair procedures after debridement" because debridement is not a repair procedure.

Oswestry point 4. How cells for ACI would be provided, if ACI were approved by NICE, is outwith our remit. However we note that the cost of cells from the NHS facility in Oswestry is lower than that of commercially-produced cells, even after including all costs. One option might be a network of regional NHS centres producing cells, or perhaps in 4th generation ACI, cartilage containing chondrocytes.

Oswestry point 5 – numbers of patients. We wonder if 300 is too low. Firstly the current NICE scope concerns symptomatic chondral defects. Some people may have temporary symptoms that resolve, but are left with chondral defects that will predispose them to later osteoarthritis (OA) and a need for knee replacement. Secondly, the current scope is limited to adults, but there is evidence on benefit in teenagers.

Oswestry point 6. We agree that the ORKA prediction tool requires external validation with larger numbers.

Oswestry point 7: ACI in the ankle. No comment – we have not reviewed that evidence on the use of ACI in the ankle.

Vericel submission of 28th July 2016.

The first Vericel submission was supportive of our assessment report WAR2 so no response necessary. However we note the comment about ACI in people with early OA. The NICE scope excludes only people with “advanced OA”.

The Riboh study is covered in WAR 3. The 5-year results from SUMMIT (academic in confidence, see below) show that 5-year KOOS results are better with ACI but they don’t contribute to long-term failure rates and hence ICERs. The numbers of failures by 5 years were small – 3 with MF and one with ACI.

Cartilage Research Foundation

This response is from one of the world leaders in cartilage repair, Tom Minas. The para starting “Dan Saris…”refers to the SUMMIT trial, and the extension study mentioned refers to the 5-year data, submitted for publication but provided to NICE and ourselves as academic in confidence, and summarised below.

ICRS undated

The Kon review mentioned by ICRS is covered in WAR 3. Carticel was originally a Genzyme product now marketed by Vericel. However Carticel is licensed for use in ACI with a periosteal cap, ACI-P, and Vericel now have FDA approval for their MACI product. So we would expect Carticel to be replaced by MACI.

SUMMIT extension study. Brittberg et al submitted for publication. Academic in confidence.

[redacted]

[redacted]

[redacted]

[redacted]

Comments from the Robert Jones & Agnes Hunt Orthopaedic & District Hospital NHS Trust (RJAH) on the Appraisal consultation document "Autologous chondrocyte implantation for repairing symptomatic articular cartilage defects of the knee (including a review of TA89)"

We thank NICE for providing us with the opportunity to comment on its draft document and preliminary recommendations. Our overall position is that we believe that ACI should be an option for NHS patients, in the context of ongoing study and development. By and large, we therefore agree with the preliminary recommendation that ACI should be undertaken within the context of further research. We realise in particular that any cost-savings from ACI over alternatives such as microfracture would come from long-term savings on subsequent treatments such as knee replacement. Solid long-term data on which to base such a decision is scarce, making a decision difficult.

We would like to make three specific comments. The first relates to the funding implications of the proposed recommendation, and the others addresses some specific aspects of our submitted data and its use in making the decision.

Comment 1

We welcome the replacement of the phrase "**not recommended** for the treatment of articular cartilage defects of the knee joint except in the context of ongoing or new clinical studies", used in the old appraisal TA89, with the proposed phrase "**recommended** only in research for repairing symptomatic articular cartilage defects of the knee". In our experience some health bodies would not read the old guidance beyond "not recommended". The proposed more positive wording seems a step forward. Nevertheless, we think the recommendation needs some further modification relating to 'only in research' because of funding implications for existing and new clinical studies.

In line with the two earlier NICE recommendations on ACI (TA16 and TA89), we have always entered our ACI patients in an ethically approved cohort study to find out their long-term results (adopted as UKCRN no. 9570). At the moment, we are still adding to that cohort study. Two years ago, we started a new randomized clinical trial of autologous cell therapies to treat knee cartilage defects, including ACI (ASCOT; UKCRN no. 12383). These studies receive funding from Arthritis Research UK, the MRC and the Orthopaedic Institute in Oswestry, a local charity funding orthopaedic research. The funds pay for the infrastructure to run these trials, such as trial management, data collection, statistical analysis etcetera, and for extra clinical investigations that are needed as part of the studies. Such funding is particularly important for long-term studies, which are the only types of study able to generate the data that NICE needs. The results from the cohort study have resulted in a steady stream of publications since we started the study in 1997 (Appendix I), which have informed understanding of and treatment with ACI. This study now starts to shine a light on the long-term results of ACI (the REACT study quoted in the appraisal consultation document).

Funding for the treatment costs in these UKCRN portfolio studies has so far come through the NHS. We are concerned that the new recommendation may halt funding for the ACI treatment costs within the context of research. This would deprive patients of a potentially effective treatment and would hinder NICE in their attempts to determine the long-term effectiveness of ACI. At some point in the future the answer may of course be found from a study performed outside England or Wales, but delegating research abroad in an attempt to

save costs does not seem prudent. Our concerns are not without ground. In our current Randomised Controlled Trial we have treated 25 patients with ACI to date. A further 3 patients (12%) could not be treated during this time period because the funding was not approved, with the response from NHS England being "NHS England does not have a formal commissioning policy in relation to this treatment. Autologous chondrocyte implantation is not routinely commissioned or funded".

The NICE assessment report shows that cell costs are a key driver of cost effectiveness. We manufacture cells within the NHS, keeping these treatment costs relatively modest. Indeed, during the first appraisal committee meeting on 10 February 2015 there was some incredulity around the table with respect to our costs, a point we will address later. One should however not forget that the ACI treatment was originally developed within an NHS-like environment in Sweden (the Gothenburg Medical Centre, Kungsbacka Hospital and Sahlgrenska University Hospital in Gothenburg). To this day, the Sahlgrenska University Hospital still manufactures the cells used for treatment in Gothenburg, for the very reasons of keeping down costs and allowing clinical research. Besides Oswestry, hospitals in Norway (Tromso) and Spain (Madrid) took the same approach. At the right costs, ACI can be cost effective, and perhaps the only way to achieve that in England and Wales is within the NHS. This is of course not without precedent, other examples of long-term successful supply of live human products from within the NHS are NHS Blood and Transplant, the Bone Marrow Transplant units around the country or the Haematopoietic Stem Cell Transplant service at University College London.

For this reason, we ask the appraisal committee to consider the following two options. The first option is for the committee to use the recommendation "research with funding" instead of "only in research". We know that this recommendation has never been used by NICE, but could be given if the expected ICER is well below the current threshold of £20k/QALY. The assessment report gives a strong indication that ACI can have an ICER of around £5k-7k per gained QALY, provided the cell production costs are £8,000 (reduced by 50%; Table 18-19 in the assessment report and Table III in Appendix II). Reducing them by 75% to £4,000 would achieve an ICER £2k-3k/QALY (Table 18-19 in the assessment report and Table III in Appendix II below). This ICER is achieved over a lifetime horizon and therefore uses many assumptions currently not supported by solid data. However, even at a shorter time horizon of 20 years ACI is likely to be cost-effective at lower cell production costs (£8.5k/QALY assuming 50% cell costs, see details in Appendix II) and even at a 10 year horizon it would be cost-effective (£13k/QALY, see details in Appendix II). At a cell cost reduction of 75%, the 10-year horizon ICER would be £5.5k/QALY (see details in Appendix II). Interestingly the latter number, based purely on the assessment group's data, is close to the ICER of £6k/QALY that was provided in our submission. That number was based on an 8-year horizon, the current follow-up in the randomised controlled trial ACTIVE, and our current treatment costs, which rely on our (lower) cell production costs. The committee could therefore consider using the recommendation "Recommended with research" adding the qualifier that cell costs in the studies should be at most 25%-50% of the cost of £16,000 assumed in the assessment report, i.e. £4,000 to £8,000. This would encourage the NHS to fund treatment costs for the studies needed to generate robust data on ACI. Moreover, our experience shows that these prices are not unrealistic within the context of an NHS manufacturing facility.

A second option for the committee would be to add a section on "Implications for the NHS", similar to the previous assessment TA89. In that section, the previous guidance read "The net

budget impact on NHS expenditure in England and Wales will depend on the number of patients in, and funding arrangements for, the clinical studies recommended in Section 1.1. The Institute expects there to be some NHS expenditure on this technology." The presence of this section in TA89 has not prevented the above mentioned difficulties in obtaining treatment funding for patients in our current UKCRN portfolio trial, indicating that it may not be sufficient. For this reason, our preferred option is for the assessment committee to use the recommendation "research with funding".

Comment 2

We were pleased that our cell production data could contribute to NICEs assessment of ACI. However, we respectfully disagree with the committee's conclusion on the true costs of the cells in section 5.16 (Cost of the cells, bottom of page 41). The current paragraph states "The Committee noted that the OsCell submission had estimated a production cost of the cells of £4125. The Committee heard from a representative of OsCell that the cost of cells included the cost of materials and staff time, but not the costs of overheads. The Committee therefore considered that OsCell had underestimated its cell costs, and that the true cost may approach that of MACI and ChondroCelect."

Our estimated cell costs of £4125 per patient did not come with a breakdown because we concentrated our submission on the total costs of the ACI procedure and its comparators as they are currently reimbursed to our hospital. We would like to use this opportunity to rectify this omission and demonstrate that, contrary to the committee's conclusion, our "true" costs do not approach the costs of MACI and ChondroCelect.

Our submitted costs were based on the annual hospital budget to run the facility, and built up as follows. The annual budget to run the facility is £150,000. This budget includes all direct running costs, hence the personnel, infrastructure, culturing etcetera. Additional costs are the annual costs for our Qualified Person (£12,000) and MHRA license fees (£3,000), bringing the total annual costs to £165,000. In a typical year, we treat 40 patients, which gave the estimated cell costs per patient of £4125.

As the committee noted, these costs did not include general overheads and depreciation costs. Our hospital finance manager estimates the overheads as £37,000 per year. Our production facilities cost around £100,000 and depreciate over 10 years, adding an extra £10,000 per year. We therefore estimate these extra costs as £47,000 per year, or £1,175 per patient. This would bring our "true" cell production costs to £5,300 per patient. As the committee will note, this cost does not approach that of MACI and ChondroCelect but amounts to 33% of the cell costs of £16,000 assumed in the committee's assessment.

To assure ourselves that our costs do not underestimate the "true" costs we asked our colleagues at hospitals in Gothenburg and Madrid, who obtain cells through similar in-house facilities, for their costs. The facility at the Sahlgrenska University Hospital in Gothenburg charges €5,500-€6,000 (£4,000-£4,400) per patient, which covers their costs. The facility in Madrid charges €2,000 (£1,500) per patient, covering their costs. In light of these figures from other facilities, we think our all-in estimate of £5,300 is unlikely to be under-priced.

Comment 3

The committee considered a possible bias in the randomised controlled trial ACTIVE with respect to rehabilitation regimes. Specifically, "the Committee considered it possible that, because of the open-label design, people having [been randomised to] ACI having been advised of the longer rehabilitation time compared to microfracture may have better adhered to rehabilitation in the hope of promised long-term benefits". We would like to comment that the results from the trial show no evidence at all of a slower rehabilitation by patients who were randomised to the ACI arm. We think this is shown most clearly by the evolution over

time of the Cincinnati Sports Activity Score, which we provided in our submission (page 25, Fig 4) and reproduce below. Rehabilitation would most strongly affect the sports activity of patients. Clearly, patients in both the ACI and control group held back from sports activity at the 3 months point to allow for their rehabilitation. At 6 months however, both groups had increased their sports activity to a level that would be largely sustained over the 4.5 ensuing years. Stronger even, the graph suggests that patients randomized to ACI had a 5 points lower baseline sports activity score, but after 6 months the sports activity scores were nearly identical in the two groups. We believe this data clearly shows that the committee's consideration that the patients randomised to ACI "may have better adhered to rehabilitation in the hope of promised long-term benefits" is not reflected in their reported activity levels. On the contrary, we think the data more likely shows that patients randomised to ACI decided to cash in early on such a promise.

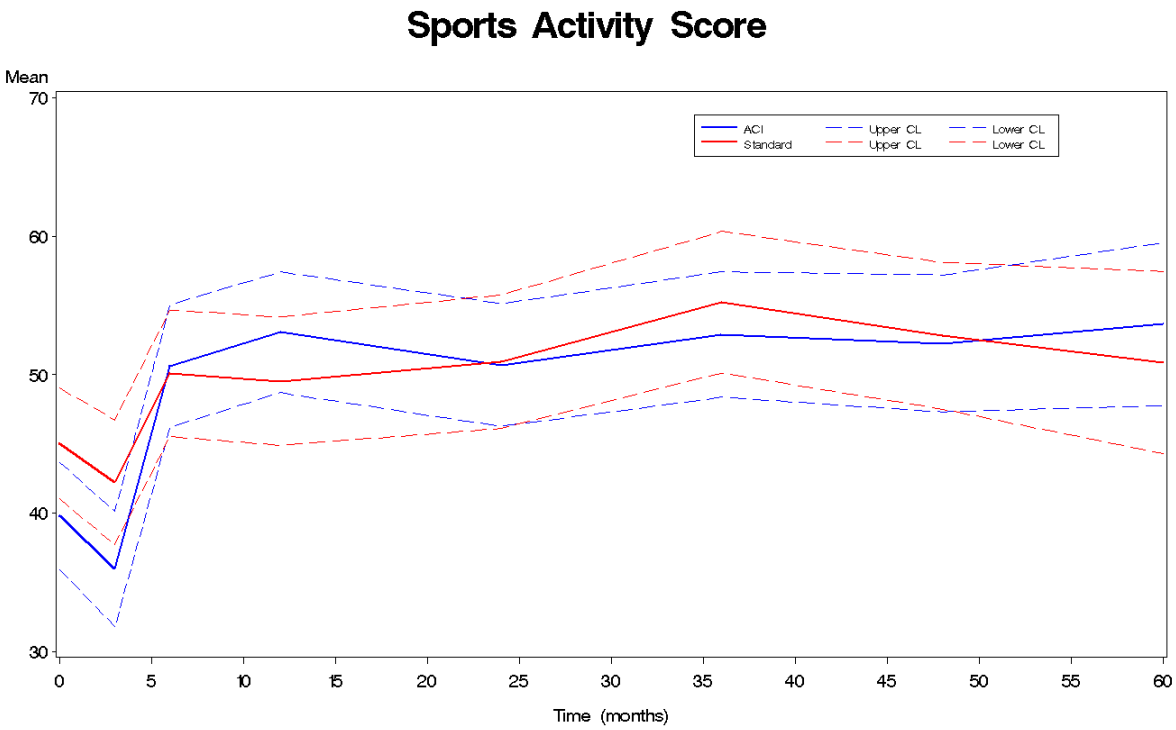

Figure 1 Evolution over time of Cincinnati Sports Activity Scale scores for patients in the ACTIVE trial randomised to ACI or "Standard" (i.e. control). 95% CIs are shown for each treatment

Appendix 1.

Peer-reviewed full publications based on our cohort study

1. BAILEY AK, MINSHULL C, RICHARDSON J, GLEESON NP (2014) Improvement of outcomes with nonconcurrent strength and cardiovascular-endurance rehabilitation conditioning after ACI surgery to the knee. J Sport Rehabil. 23(3):235-43

2. WRIGHT KT, MENNAN C, FOX H, RICHARDSON JB, BANERJEE R, ROBERTS S (2013) Characterization of the cells in repair tissue following autologous chondrocyte implantation in mankind: a novel report of two cases. Regenerative Medicine 8:699-709.

3. McCARTHY HS and ROBERTS S (2013) A Histological Comparison of the Repair Tissue Formed When Using Either Chondrogide® or Periosteum during Autologous Chondrocyte Implantation. Osteoarthritis and Cartilage: 21(12):2048-57.

4. HANIFI A, MCCARTHY H, ROBERTS S & PLESHKO N. (2013) Fourier Transform Infrared Imaging and Infrared Fiber Optic Probe Spectroscopy Identify Collagen Type in Connective Tissues. PLoS ONE 8(5): e64822. doi: 10.1371/journal.pone.0064822

5. JOHNSON B, LEVER C, ROBERTS S, RICHARDSON J, MCCARTHY H, HARRISON P, LAING P, MAKWANA N (2013). Cell cultured chondrocyte implantation and scaffold techniques for osteochondral talar lesions. Foot Ankle Clin. 18(1):135-50.

6. MCCARTHY HS, MALDA J, RICHARDSON JB, ROBERTS S. (2013) Increased Production of Clusterin in Biopsies of Repair Tissue following Autologous Chondrocyte Implantation. Cartilage 4(3):227-238 doi:10.1177/1947603513477652

7. KHAN M, ROBERTS S, RICHARDSON JB, MCCASKIE AW. (2013) Stem cells and orthopaedic surgery. Bone & Joint 360: 2:2-5 doi:0105.21.360107

8. KARTHIKEYAN S, ROBERTS S, GRIFFIN D. (2012) Microfracture for acetabular chondral defects in patients with femoro- acetabular impingement: Results at second-look arthroscopy. American Journal of Sports Medicine: 40(12):2725-30

9. HANIFI A, RICHARDSON J, KUIPER JH, ROBERTS S*, PLESHKO N* (joint last author). (2012) Clinical Outcome of Autologous Chondrocyte Implantation Is Correlated With Infrared Spectroscopic Imaging-Derived Parameters. Osteoarthritis and Cartilage 20(9):988-96

10. LUTIANOV M, NAIRE S, ROBERTS S, KUIPER JH. (2011) A mathematical model of cartilage regeneration after cell therapy. J Theor Biol. 289:136-50.

11. ROBERTS S, GENEVER P, MCCASKIE A, DE BARI C. (2011) Prospects of stem cell therapy in osteoarthritis. Regenerative Medicine 6:351-356

12. HOEMANN CD, KANDEL R, ROBERTS S, SARIS DBF, CREEMERS L, MAINIL-VARLET P, MÉTHOT S, HOLLANDER AP, BUSCHMANN MD (2011) Recommended guidelines for histological endpoints for cartilage repair studies in animal models and clinical trials. Cartilage 2:153-172

13. KAY A, RICHARDSON J, FORSYTH NR (2011) Physiological normoxia and chondrogenic potential of chondrocytes. Front Biosci 3:1365-74

14. ROBERTS S, MENAGE J, FLANNERY CR, RICHARDSON JB (2010) Lubricin: Its Presence In Repair Cartilage Following Treatment With Autologous Chondrocyte Implantation. Cartilage 1: 298 –305

15. MAINIL-VARLET P, VAN DAMME B, NESIC D, KNUTSEN G, KANDEL R, ROBERTS S. (2010) A new histology scoring system for the assessment of the quality of human cartilage repair: ICRS II. Am J Sports Med. 2010 May;38(5):880-90.

16. SMITH HJ, RICHARDSON JB, TENNANT A (2009) Modification and validation of the Lysholm Knee Scale to assess articular cartilage damage. Osteoarthritis Cartilage 17(1):53-8

17. BHOSALE AM, KUIPER JH, JOHNSON WE, HARRISON PE, RICHARDSON JB. (2009) Midterm to long-term longitudinal outcome of autologous chondrocyte implantation in the knee joint: a multilevel analysis. Am J Sports Med. 37 Suppl 1:131S-8S.

18. ROBERTS S, MENAGE J, SANDELL LJ, EVANS EH, RICHARDSON JB. (2009) Immunohistochemical study of collagen types I & II and procollagen IIA in human cartilage repair tissue following autologous chondrocyte implantation. The Knee 16:398-404

19. BHOSALE AM, RICHARDSON JB (2008) Articular cartilage: structure, injuries and review of management. Br Med Bull. 87:77-95.

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21. GLASER C, TINS BJ, TRUMM CG, RICHARDSON JB, REISER MF, MCCALL IW (2007) Quantitative 3D MR evaluation of autologous chondrocyte implantation in the knee: feasibility and initial results. Osteoarthritis Cartilage 15(7):798-807.

22. BHOSALE AM, MYINT P, ROBERTS S, MENAGE J, HARRISON P, ASHTON B, SMITH T, McCALL I, RICHARDSON JB. (2007) Combined autologous chondrocyte implantation and allogeneic meniscus transplantation: A biological knee replacement. The Knee 14:361-8

23. KNUTSEN G, DROGSET JO, ENGEBRETSEN L, GRANTVEDT T, ISAKSEN V, LUDVIGSEN TC, ROBERTS S, SOLHEIM E, STRAND T, & JOHANSEN O (2007) A Randomized Trial Of ACI Versus Microfracture. The Picture At Five Years. J Bone Joint Surg (Am) 89: 2105-12

24. GUPTA A, BHOSALE A, BALBOUZIS T, SMITH HJ, RICHARDSON JB (2006) Cartilage transplantation. Br J Hosp Med 67(6):286-9.

25. TAKAHASHI T, TINS B, MCCALL IW, RICHARDSON JB, TAKAGI K, ASHTON K (2006) MR appearance of autologous chondrocyte implantation in the knee: correlation with the knee features and clinical outcome. Skeletal Radiol. 35(1):16-26.

26. AKIMAU P, BHOSALE A, HARRISON PE, ROBERTS S, MCCALL IW, RICHARDSON JB, ASHTON B (2006) Autologous chondrocyte implantation with bone grafting for osteochondral defect due to posttraumatic osteonecrosis of the hip – a case report. Acta Orthop Scand 77:333-336

27. SMITH GD, TAYLOR J, ALMQVIST KF, ERGGELET C, KNUTSEN G, GARCIA PORTABELLA M, SMITH T, RICHARDSON JB (2005). Arthroscopic assessment of cartilage repair: a validation study of 2 scoring systems. Arthroscopy 21(12):1462-7

28. WHITTAKER J-P, SMITH G, MAKWANA N, ROBERTS S, HARRISON PE, LAING P & RICHARDSON JB. (2005) Early Results of Autologous Chondrocyte Implantation in the Talus. J Bone Joint Surg 87B:179-183.

29. SMITH GD, KNUTSEN G, RICHARDSON JB (2005) A clinical review of cartilage repair techniques. J Bone Joint Surg Br. 87(4):445-9

30. TINS BJ, MCCALL IW, TAKAHASHI T, CASSAR-PULLICINO V, ROBERTS S, ASHTON B & RICHARDSON J (2004) Autologous Chondrocyte Implantation in Knee Joint: MR Imaging and Histologic Features at 1-Year Follow-up. Radiology 234:501-508.

31. KNUTSEN G, ISAKSEN V, ENGEBRETSEN L, LUDVIGSEN TC, DROGSET JO, GRØNTVE T, SOLHEIM E, STRAND T, ROBERTS S & JOHANSEN O. (2004) A randomized trial of autologous chondrocyte implantation versus microfracture in the knee. J Bone Joint Surg 86A: 455-464.

32. MAINIL-VARLET P, AIGNER T, BRITTBERG M, BULLOUGH P, HOLLANDER A, HUNZIKER E, KANDEL R, NEHRER S, PRITZKER K, ROBERTS S, STAUFFER E. (2003) Histological Assessment of Cartilage Repair, A report by the histological endpoint committee of the international cartilage repair society (ICRS). J Bone Joint Surg 85-A Suppl 2 45-57.

33. HARRISON PE, PFEIFER PM, TURNER SL, RICHARDSON JB, JONES PW, ASHTON BA (2003) Serum from patients anesthetized with opiates less effective in the support of chondrocyte growth in vitro. Tissue Eng. 9(1):37-9

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36. ROBERTS,S, HOLLANDER,AP, CATERSON,B, MENAGE,J, & RICHARDSON,JB. (2001) Matrix turnover in human cartilage repair tissue in autologous chondrocyte implantation, Arthritis and Rheumatism, 44, pp.2586-2598.

37. HARRISON PE, ASHTON IK, JOHNSON WE, TURNER SL, RICHARDSON JB, ASHTON BA (2000) The in vitro growth of human chondrocytes. Cell Tissue Bank 1(4):255-60

38. RICHARDSON,JB, CATERSON,B, EVANS,EH, ASHTON,BA, & ROBERTS,S. (1999) Repair of human articular cartilage after implantation of autologous chondrocytes, Journal Bone and Joint Surgery, 81-B, pp.1064-1068.

Appendix II

Calculation of ICERs at shorter time horizons (10 and 20 years) and reduced cell costs

The assessment report on autologous chondrocyte implantation for repairing symptomatic articular cartilage defects of the knee, prepared by Warwick Evidence, assumes a cell cost of £16,000. Based on these cell costs, the costs of two consecutive cartilage treatments vary from £5,015 to £20,921 (Table 17 in the report, partly reproduced in Table I below, base-case costs).

Table I. Total mean costs and the QALYs gained of four scenarios considered in the assessment report. Mean costs are given for three different cell costs, and QALYs gained for three different time horizons

	Costs			QALYs gained		
Scenario	Base-case costs	Cell costs 50% lower	Cell costs 75% lower	Lifetime horizon	20 year horizon	10 year horizon
1: MF (MF)	5,015	5,015	5,015	17.00	11.26	7.29
2: MF (ACI)	6,607	5,760	5,336	17.03	11.28	7.30
3: ACI (MF)	19,892	11,892	7,892	17.96	12.07	7.83
4: ACI (ACI)	20,921	12,373	8,100	18.02	12.10	7.85

Note: Costs and QALYs gained were compiled from Tables 17, 19 and 21 in the assessment report, using values from the deterministic model

The four scenarios in the table correspond to four scenarios considered in the report, namely:
(1) Microfracture (MF), which fails at some point and is followed by a further MF
(2) Microfracture (MF), which fails at some point and is followed by ACI
(3) ACI, which fails at some point and is then followed by a microfracture (MF)
(4) ACI, which fails at some point and is then followed by a further ACI

In its sensitivity study, the assessment report also gives the costs for the four scenarios at reduced cell costs (Table 19, partly reproduced in Table I). The report further provides the QALYs gained for the four above scenarios, at the base-case time horizon (lifetime horizon starting at age 33; Table 17, partly reproduced in Table I) and at shorter time horizons (10 and 20 years; Table 21, partly reproduced in Table I).

These numbers can be used to determine Incremental Cost Effectiveness Ratios (ICERs) compared to the baseline scenario (1) of two microfractures. Assuming a lifetime horizon, the ICER is £63,426 per QALY for scenario 2, and £15,600 per QALY for scenarios 3/4 (Table II below). The numbers for the latter two scenarios are close to and that for scenario 2 well above the current ICER threshold of £20,000/QALY.

Table II. ICER for different scenarios involving ACI compared to a baseline scenario involving only MF, assuming cell costs of £16,000

		Lifetime horizon		20 year horizon		10 year horizon	
Scenario	Increm costs	Increm QALYs	ICER	Increm QALYs	ICER	Increm QALYs	ICER
1: MF (MF)	-	-	-	-	-	-	-
2: MF (ACI)	1,592	0.03	63,426	0.02	70,756	0.01	128,387
3: ACI (MF)	14,877	0.95	15,599	0.81	18,442	0.54	27,474
4: ACI (ACI)	15,906	1.02	15,602	0.85	18,817	0.55	28,670

Note: Values for the incremental costs and incremental QALYs were based on the values compiled in Table I

The lifetime horizon uses many assumptions, such as conversion of the cartilage repair to a knee prosthesis. Looking at shorter time horizons reduces this reliance on assumptions, but will increase the ICERs. At 10 year, the ICER of scenario 2 is £128,387/QALY and that of the two ACI-first scenarios is around £28,000/QALY, all compared to scenario 1 (Table II). These 10-year ICERs are all well above the threshold of £20,000/QALY.

Cell costs form a main driver of the ICER, and reducing these costs therefore drastically reduces the ICER. If cell costs were reduced to £8,000 (a 50% reduction), then the ICER of the two ACI first scenarios would be around £7,200/QALY at a lifetime horizon and around £13k/QALY at a 10 year horizon (Table III). If cell costs were further reduced to £4,000 (a 75% reduction), the ICER of the two ACI-first scenarios would be around £3k/QALY at a lifetime horizon and around £5,500 at a 10 year horizon (Table III).

Table III. ICER for different scenarios involving ACI compared to a baseline scenario involving only MF, assuming cell costs of £8,000 (50% lower) and £4,000 (75% lower).

		Lifetime horizon		20 year horizon		10 year horizon	
Scenario	**Increm costs**	**Increm QALYs**	**ICER**	**Increm QALYs**	**ICER**	**Increm QALYs**	**ICER**
Cell costs £8,000 (50% lower)							
1: MF (MF)	-	-	-	-		-	-
2: MF (ACI)	745	0.03	29,681	0.02	33,111	0.01	60,081
3: ACI (MF)	6,877	0.95	7,211	0.81	8,525	0.54	12,700
4: ACI (ACI)	7,358	1.02	7,217	0.85	8,705	0.55	13,262
Cell costs £4,000 (75% lower)							
1: MF (MF)	-	-	-	-		-	-
2: MF (ACI)	321	0.03	12,789	0.02	14,267	0.01	25,887
3: ACI (MF)	2,877	0.95	3,017	0.81	3,566	0.54	5,313
4: ACI (ACI)	3,085	1.02	3,026	0.85	3,650	0.55	5,561

Note: Values for the incremental costs and incremental QALYs were based on the values compiled in Table I

Autologous chondrocyte implantation for repairing symptomatic articular cartilage defects of the knee (including a review of TA89) – Sobi response to Appraisal Consultation Document (ACD)

The recommendation for use only in research given in the appraisal consultation document (ACD) is an understandable decision in the context of OsCell (for which there is no published outcome or safety data), given the product is unlicensed. However this may not be the most appropriate decision for ChondroCelect and MACI. Given no new data will be available in the near future, Sobi are disappointed by the Committee's provisional decision and feel that, with no ongoing trials, it effectively represents a negative recommendation for ChondroCelect.

On further reflection of the available evidence, three important issues were not raised in the ACD.

- Firstly, while the ACTIVE trial (based in the OsCell centre) is due to provide ten year data, it is a non-randomised study with a 'pragmatic comparator' arm. The quality of its data is uncertain, and patient numbers in the long term are likely to be low (with potentially informative dropout). While efficacy results were not presented, the utility data presented were not of a high standard.
- Secondly, although MACI has a well conducted randomised controlled trial with several years follow up, the marketing authorisation for this product is currently suspended (and has been since December, 2014).
- Finally, the marketing authorisation for ChondroCelect is misrepresented in section 5.6 of the ACD. Although the trial for ChondroCelect is in patients with a lesion size of up to $5cm^2$, the license allows treatment of all patients – in the Belgian registry data, 40% of patients had lesions over $5cm^2$.

For ChondroCelect, the pivotal randomised trial, TIG/ACT/01/2000, provides data to five years. This is much more than the majority of interventions assessed by NICE and, as stated by the assessment group, is a high quality study. The final five year reporting from this study has also completed (the initial study was powered for twelve month outcomes). With no ongoing trials for ChondroCelect, use in research would require the establishment of a registry.

Sobi understand that the Committee was faced with uncertainty regarding the most appropriate economic modelling of the disease area (though the Sobi manufacturer's model was closest to the clinical practice), as well as uncertainty on long term treatment effectiveness. To this end, we have provided additional data and analyses where issues have been raised in the ACD, issues identified by the committee, and sensitivity analyses around uncertainties. We hope that these may provide the basis for a positive recommendation to be made.

Our revised modelling (with all changes suggested by the committee), and including more appropriate modelling of effectiveness (parametric curve fitting), provides an incremental cost-effectiveness ratio (ICER) of £25,961 compared to microfracture. The ICER is £14,727 using a discount rate of 1.5% to account for the long term benefits of ACI. Likewise excluding treatment failures due to the old technique used in the trial, the ICER falls to £18,500. The major changes generating this new ICER are:

- New analysis of SF-36 data collected in the TIG/ACT trial (now mapped to EQ-5D)
- Revised utility values for patients who did not receive a re-intervention (identified by the committee)
- Including a minimum age restriction for knee replacement, and the possibility of a partial replacement
- Changes to unit costs
- An exploratory comparison with MACI
- Extrapolation of treatment failure using parametric curves (not a line of best fit)

We hope that our additional analyses and modelling are sufficient for the Committee to issue a positive final recommendation. However if a use in research recommendation is viewed by the Committee as being the most appropriate, Sobi request that a third Appraisal Committee meeting be held with a gap of at least 8 weeks from the publication of any decision. This will allow Sobi the chance to organise the creation of a registry, which can then be used to collect longer term data, if viewed as sufficient by the NICE Committee. This will ensure that both use and research do happen, and without which, the decision would effectively be a 'no'.

Autologous chondrocyte implantation for repairing symptomatic articular cartilage defects of the knee (including a review of TA89) – Sobi response to Appraisal Consultation Document (ACD)

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MODEL REVISIONS

UTILITY VALUES: FORMAL ANALYSIS OF TIG/ACT DATA

In section 5.18 of the ACD, the Committee conclude that the source of utility values used in both the Sobi model and assessment group model lacked transparency, with no details of the dataset used. The utility data that were used in both models were taken from a publication by Gerlier et al (2010), presenting their analysis of the TIG/ACT data.

In examining the paper, Sobi are also unclear on the exact source and method of the values used, and have therefore reanalysed the SF-36 from TIG/ACT. For our analysis the SF-36 data were mapped to EQ-5D values using the Rowen et al (2011) algorithm. The SF-36 questionnaire was administered at routine follow-up visits during the post-12 months study phase, with the first possible at 18 months post-intervention. At the 18 month visit only one patient completed the questionnaire; therefore the mapped utility results presented below are from the 24 month visit onwards.

Over the course of 36 months of SF-36 follow-up, mean mapped utility fluctuated between 0.802 and 0.834. Fourteen patients completed the questionnaire at 24 months, rising to 58 patients at 60 months. ChondroCelect patients reported consistently higher utility values across the time period. The mean utility value for patients who were defined as KOOS responders was much larger than KOOS non-responders across the time period, albeit with generally few KOOS non-response observations.

Table 1: Utilities mapped from TIG/ACT/01 SF-36 data using the Rowen algorithm

Patients	Outcome	24 months	30 months	36 months	48 months	60 months
Analysed by treatment arm						
ChondroCelect patients	Mean utility	**0.817**	**0.861**	**0.849**	**0.820**	**0.833**
	Standard d.	0.126	0.182	0.193	0.177	0.169
	Observations	10	16	19	30	27
Microfracture patients	Mean utility	**0.793**	**0.806**	**0.810**	**0.783**	**0.775**
	Standard d.	0.249	0.191	0.192	0.209	0.181
	Observations	4	12	20	25	31
Analysed by KOOS response status						
KOOS response*	Mean utility	**0.854**	**0.888**	**0.911**	**0.864**	**0.845**
	Standard d.	0.110	0.166	0.135	0.137	0.160
	Observations	9	17	25	40	41
KOOS non-response*	Mean utility	**0.736**	**0.740**	**0.683**	**0.633**	**0.719**
	Standard d.	0.248	0.188	0.193	0.232	0.177
	Observations	4	10	14	13	15
All patients						
All patients	Mean utility	**0.810**	**0.834**	**0.830**	**0.803**	**0.802**
	Standard d.	0.519	0.184	0.189	0.191	0.176
	Observations	14	28	40	55	58

* As per CSR: response defined as an increase in overall KOOS of at least 10 percentage points and/or an increase of at least 10 percentage points in at least three of the four (except sports) subdomains.
Key: KOOS, Knee Injury and Osteoarthritis Outcome Score.

While these results suggest that ChondroCelect and KOOS response improve utility, a generalised estimating equation (GEE) regression was performed in order to account for correlation of utility values provided by the same individual at different assessments. Covariates included as potential predictors of utility were:

- Gender
- Intervention (ChondroCelect or microfracture)

- Onset of symptoms <3 years prior to intervention
- KOOS response status (response or non-response)

Intervention and the binary variable for time since onset of symptoms <3 years were dropped as insignificant predictors, leaving the regression model presented in Table 2. The results suggest that experiencing a KOOS response leads to a 0.11 improvement in utility. Additionally, male respondents (134/195 total questionnaire responses) reported better quality of life than female TIG/ACT participants.

Table 2: GEE regression results for utility values derived from TIG/ACT

Variable	Coefficient	P value
Constant term	0.5906830	0.0369311
KOOS response = Yes	0.1110939	0.0362757
Gender = Male	0.1855282	0.2814180
Key: KOOS, Knee Injury and Osteoarthritis Outcome Score.		

These utility values obtained have been included in the model, and are used in the revised base case analysis. As a result, the revised model does not make any use of the values from the Gerlier et al study that were questioned in the ACD (Table 3).

Table 3: Revised health state utilities used in model

Health state	Original utility value	Revised utility value	Assumption
Baseline (pre-intervention)	0.6540	Male: 0.7762 Female: 0.5907	Assumed equal to non-response
Resolved (successful first repair)	0.8170	Male: 0.8873 Female: 0.7012	GEE regression
Receiving debridement and BSC	0.6910	Male: 0.7762 Female: 0.5907	GEE regression
Undergoing knee replacement	0.5177	0.5177	No change
Successful knee replacement	0.6830	0.7300	NHS PROMS selected
Unresolved defect	0.5570	0.5200	Ruchlin OA value assumed
Key: GEE, generalised estimating equation; PROMS, patient-reported outcome measures; OA, osteoarthritis.			

APPLICATION OF UTILITY VALUES TO SUCCESSFUL REPAIR

In section 5.8 of the ACD, the Committee note that the Sobi cost-effectiveness model defined treatment failure according to the need for re-intervention on the index lesion. The Committee highlight that by doing so the model assumed all patients who had not received a re-intervention were therefore defined as a treatment success (which may not be the case). The committee concluded this was *"likely to overestimate considerably the time spent in the successful primary repair state"*. Sobi agree with this assessment, and have revised the values used accordingly.

In order to rectify this, the proportion of patients not receiving a re-intervention who were *also* KOOS responders, was extracted from the TIG/ACT patient-level data (Table 4). In the revised model, only this proportion of patients experience the 0.11 utility increase associated with KOOS response. The remainder do not and are therefore considered KOOS non-responders, despite not having required a re-intervention.

For example, at 12 months, 72.5% of ChondroCelect patients who had not received a re-intervention were KOOS responders. Therefore, for the model time period from 12 months to the next follow-up visit (18 months), 72.5% of successful ChondroCelect patients experience the 0.11 utility benefit.

Table 4: Proportion of non-re-intervention patients who were also KOOS responders

TIG/ACT assessment	Percentage of patients with no re-intervention who were KOOS responders		Time period applied for in revised model
	ChondroCelect	Microfracture	
2 months	65.3%	57.6%	0-3 months
3 months	64.7%	62.7%	3-6 months
6 months	70.6%	69.5%	6-9 months
9 months	76.5%	69.6%	9-12 months
12 months	72.5%	73.7%	12-18 months
18 months	72.1%	71.4%	18-24 months
24 months	81.8%	66.7%	24-30 months
30 months	73.2%	64.4%	30-36 months
36 months	82.1%	65.1%	36-48 months
48 months	76.9%	71.1%	48-60 months
60 months	75.0%	70.0%	60+ months

Key: KOOS, Knee Injury and Osteoarthritis Outcome Score.

In making this revision, the model is no longer simply focused on whether or not their defect has received another intervention, and takes in to account the outcomes experienced by patients.

PARAMETRIC MODELLING OF TREATMENT FAILURE

The Sobi model extrapolated beyond the observed TTF data by using a 'straight line', assuming a constant failure gradient over time. Although not prompted by the Committee or ACD, on reflection this approach to extrapolating efficacy data was too simplistic, and did not take into account the change in patient numbers over time in the trial when fitting the curves.

We have therefore revised the model by fitting parametric survival curves to time to treatment failure (TTF). Parametric modelling is a more sophisticated method of extrapolating beyond the observed data, representing better practice and unequivocally improving the long term projections of the model. Although this causes a marked deterioration in the ICER for ChondroCelect, scientifically this is the most appropriate method.

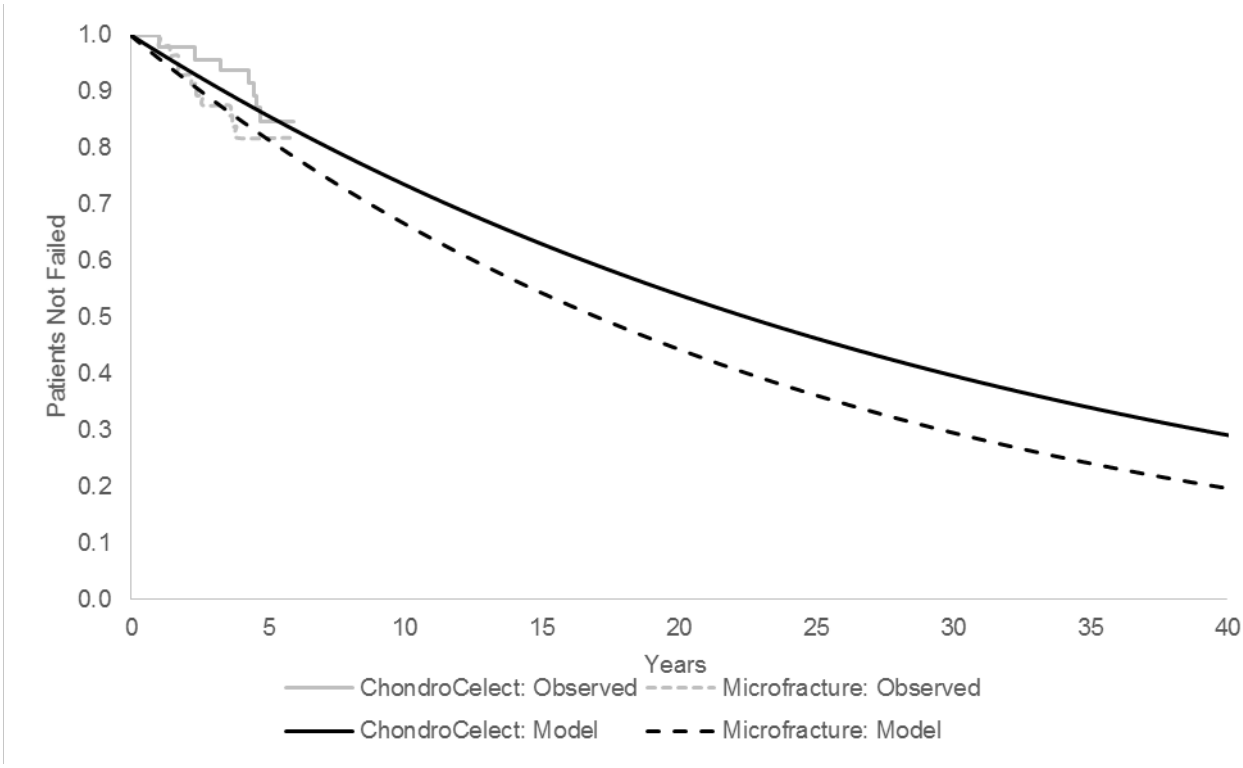
Exponential, Gompertz, log-logistic, log-normal and Weibull functions were fitted to the TTF data. Due to the small number of failures observed (N=7), only the exponential model was able to provide a reasonable fit to the ChondroCelect data. The exponential distribution provided the best fit to the microfracture TTF data using the Bayesian Information Criterion, and second-best based upon the Akaike Information Criterion. As it therefore provides a good statistical fit to the data, the exponential model was also selected to characterise microfracture TTF, in order to provide a fair comparison with ChondroCelect.

The exponential TTF model parameters are provided in Table 5, and the resulting curves are presented in Figure 1.

Table 5: Exponential survival curve parameters used to characterise TTF in the revised model

Arm	Exponential coefficient	Standard error	Resulting constant failure rate
ChondroCelect	-3.478886	0.3779645	0.26% per month
Microfracture	-3.200646	0.3162278	0.34% per month

Figure 1: Exponential survival curves applied in the revised model



While this analysis provides a more methodologically sound approach to extrapolating beyond the observed failure data, we would like to reiterate that the TIG/ACT failure results for ChondroCelect are likely to the higher than the clinical reality.

As noted in section 4.6 of the ACD, ChondroCelect in the trial used the now outdated first-generation ACI procedure. The state of the art has evolved, with second- and third-generation ACI, and no failures due to loosening are reported in current clinical practice – this contrasts with 4 of the 7 failure in the TIG/ACT trial being due to loosening of the flap. Accounting for this lower failure rate would increase the delta between the treatments in favour of ChondroCelect. An exploratory estimate of the likely ICER is presented as a scenario analysis in this response.

CLINICAL PATHWAY INCLUDED IN THE MODEL

In section 5.9 of the ACD, the Committee note clinical advice that knee replacement surgery is only considered as a salvage treatment, particularly in people younger than 55 years. The results of a scenario analysis performed by Sobi were heard at the meeting whereby no knee replacement surgeries were permissible before the age of 55 years, as reported in section 5.13. This assumption has been formally included in the revised base case cost-effectiveness analysis.

Also in section 5.9, the Committee conclude that both the Sobi and AG models do *"not accurately reflect the treatment pathway in clinical practice."* Sobi would like to assert that this conclusion is unwarranted as, with the

exception of the age at which knee replacement can occur, the Sobi model does in fact reasonably reflect the clinical pathway described in section 5.9:

- The model compares to microfracture, the comparator in clinical practice, acknowledged in section 5.2 of the ACD
- The model does allow for a second repair procedure, namely microfracture, in both arms
- A second microfracture is less likely to be used following an initial microfracture, based upon clinical expert advice due to a lack of confidence in its efficacy the second time (also highlighted by clinical experts at the meeting, see ACD section 5.9)
- Patients in the model must pass through a period of receiving debridement and best supportive care before they are considered for knee replacement surgery. They do not skip this phase and go straight from a repair intervention to knee replacement surgery. Prior to surgery, patients will have undergone at least one debridement treatment (two if they had received a second microfracture).
- The base case model has now been revised to restrict knee replacement surgery to patients aged 55 or over

The only discrepancy is the absence of osteotomy from the Sobi model; however in the absence of osteotomy-specific evidence we are unable to adequately include this. The likely outcome of doing so would be an increase in costs in treatment failures (higher in the microfracture arm), so would favour ChondroCelect.

Despite the absence of osteotomy, the Sobi model still provides a reasonable estimation of clinical practice, and a better reflection of clinical practice than the assessment group model in which all patients are assumed to receive a second treatment, which has the same efficacy as first line treatment. This assumption is not borne out by either trial evidence, or the expert opinion heard by the Committee. Furthermore, the assessment group model assumes 100% of patients receive second line treatment, which is not representative of clinical practice.

UNIT COSTS AND HRG CODES

The Committee provided alternative unit costs for the ChondroCelect procedure (section 5.15 of the ACD), based upon more accurate HRG codes.

Although we have been unable to verify these figures, we have used the suggested unit cost of £870 for cell harvest (day case, HB25F) and £2,396 for cell implantation (day case, HB22C).

INCLUSION OF MACI AS A COMPARATOR

As we have no evidence (direct or indirect) to compare against MACI, we recognise that it is an approved treatment with high quality clinical evidence. It has there been included in the Sobi model, assuming equal efficacy to ChondroCelect, supported by the indirect comparison by the MACI manufacturer discussed in section 4.16 of the ACD. ICERs are presented against microfracture using the MACI list price.

Threshold analyses are also provided to understand how much more effective than ChondroCelect MACI would need to be to be cost-effective in a full incremental analysis. While we do not necessarily suggest incremental analyses be made between products, the results from the ChondroCelect model we hope will allow the committee to compare the Sobi model results to the assessment group model results, and may also inform the committee's decision making on MACI.

REVISED COST-EFFECTIVENESS RESULTS

The revisions made the model documented in this ACD response build upon the amendments detailed in our response to the assessment report and, where applicable, supersede all previously provided results as being a more accurate representation of the cost-effectiveness of ChondroCelect. Previous results therefore should not be cited, as these are outdated.

The revised model results are provided below, along with how the ICER changed to this new value, as well as key sensitivity analyses. Sobi hopes that these results will increase the Committee's confidence in estimating the cost-effectiveness of ChondroCelect, and lead to a positive final recommendation.

CHANGES TO THE MODEL MADE INDIVIDUALLY

Table 6 presents the individual effect of each model change on the original base case ICER submitted (£6,997).

Each of the requested changes causes a modest increase in the ICER when made individually. Incorporating partial knee replacements, as initially suggested by the assessment group (see section 4.31 of the ACD) increases it slightly to £7,406. Using our revised utility values, and applying them separately for KOOS responders and non-responders, provides an ICER of £9,133. Revising the unit costs as suggested in section 5.15 of the ACD raises the ICER to £9,269. The largest individual effect is caused by restricting knee replacements to patients aged 55 years or older, with a resulting ICER of £10,799.

When all of these changes are made simultaneously, the ICER is £20,046. This remains well within the range typically considered cost-effective.

The additional change made to the model was to characterise TTF using a parametric curve fitted to the data, rather than assuming a linear failure rate beyond the observed data. While this change was not requested by the Committee, we believe it to be a more scientifically correct approach to extrapolation. Including this amendment, the revised base case ICER is £25,961.

Table 6: Cost-effectiveness results applying each model revision individually

Change made	Base case ICER	New ICER
Submitted base case	£6,997	-
Partial knee replacement included	£6,997	£7,406
Revised utility estimates	£6,997	£9,133
Knee replacement minimum age restriction: 55 years	£6,997	£10,799
Revised unit costs	£6,997	£9,629
All requested changes made		**£20,046**
Parametric forms used for efficacy data	£6,997	£10,493
All changes made including parametric TTF data (new base case)		**£25,961**
Key: ICER, incremental cost-effectiveness ratio; TTF, time to treatment failure.		

DISAGGREGATED BASE CASE RESULTS

In the revised base case model, ChondroCelect is associated with an ICER of £25,961 per additional QALY, compared to microfracture. While this is higher than the analysis originally submitted, it is still within the range typically considered by NICE to represent a cost-effective intervention.

Table 7: Revised base case model cost-effectiveness results, 3.5% discount rate

Model arm	Total			Incremental			ICER
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Microfracture	£8,086	23.09	15.85				
ChondroCelect	£24,324	23.16	16.48	£16,238	0.07	0.63	**£25,961**
Key: ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years.							

Table 8: Revised base case model, disaggregated discounted cost results, 3.5% discount rate

Cost item	Microfracture	ChondroCelect	Increment
Procedure (including rehabilitation)	£3,020	£20,528	£17,508
Secondary treatments (MFx, debridement)	£878	£1,858	£980
KR (inc. assessments & revisions)	£3,873	£1,790	-£2,083
Treatment of unresolved patients	£315	£148	-£168
Total costs	**£8,086**	**£24,324**	**£16,238**
Key: MFx, microfracture; KR, knee replacement.			

As noted in the original Sobi submission, ACI is an intervention for which it may be appropriate to discount outcomes a rate lower than 3.5%. The NICE Methods Guide (section 6.2.19) stipulates that a lower uniform discount rate of 1.5% may be suitable where health outcomes are improved over a very long period.

Successful knee cartilage repair with ChondroCelect is effectively curative, all but eliminating the need for future intervention and knee surgery, and allowing patients a return to normal activities, including high level sport. It is therefore relevant to consider the cost-effectiveness results with annual discounting at 1.5% for ChondroCelect. With this change the ICER is highly cost-effective, at £14,727 per additional QALY gained, largely due to a gain of 1.00 additional QALY.

Table 9: Revised base case model cost-effectiveness results, 1.5% discount rate

Model arm	Total			Incremental			ICER
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Microfracture	£12,032	33.39	22.25				
ChondroCelect	£26,780	33.55	23.25	£14,749	0.16	1.00	**£14,727**
Key: ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years.							

Table 10: Revised base case model, disaggregated discounted cost results, 1.5% discount rate

Cost item	Microfracture	ChondroCelect	Increment
Procedure (including rehabilitation)	£3,020	£20,528	£17,508
Secondary treatments (MFx, debridement)	£1,154	£2,490	£1,337
KR (inc. assessments & revisions)	£7,114	£3,402	-£3,711
Treatment of unresolved patients	£745	£360	-£385
Total costs	**£12,032**	**£26,780**	**£14,749**
Key: MFx, microfracture; KR, knee replacement.			

SENSITIVITY ANALYSIS

Probabilistic sensitivity analysis (PSA) was performed in order to present the robustness of the base case ICER to parameter uncertainty, by comparing the results of 1,000 probabilistic model iterations with the deterministic results above. With uniform discounting of 3.5% per year, the PSA ICER is £25,539 per additional QALY. With uniform discounting of 1.5% per year, the PSA ICER is £14,378 per additional QALY.

Figure 2: Results from 1,000 probabilistic model runs, 3.5% discount rate

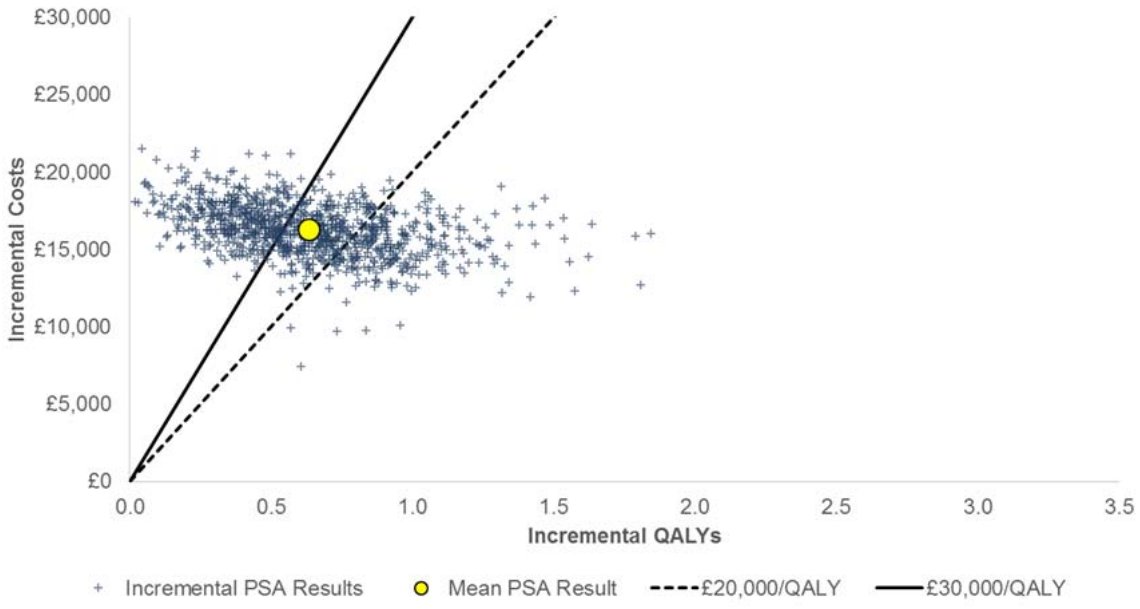
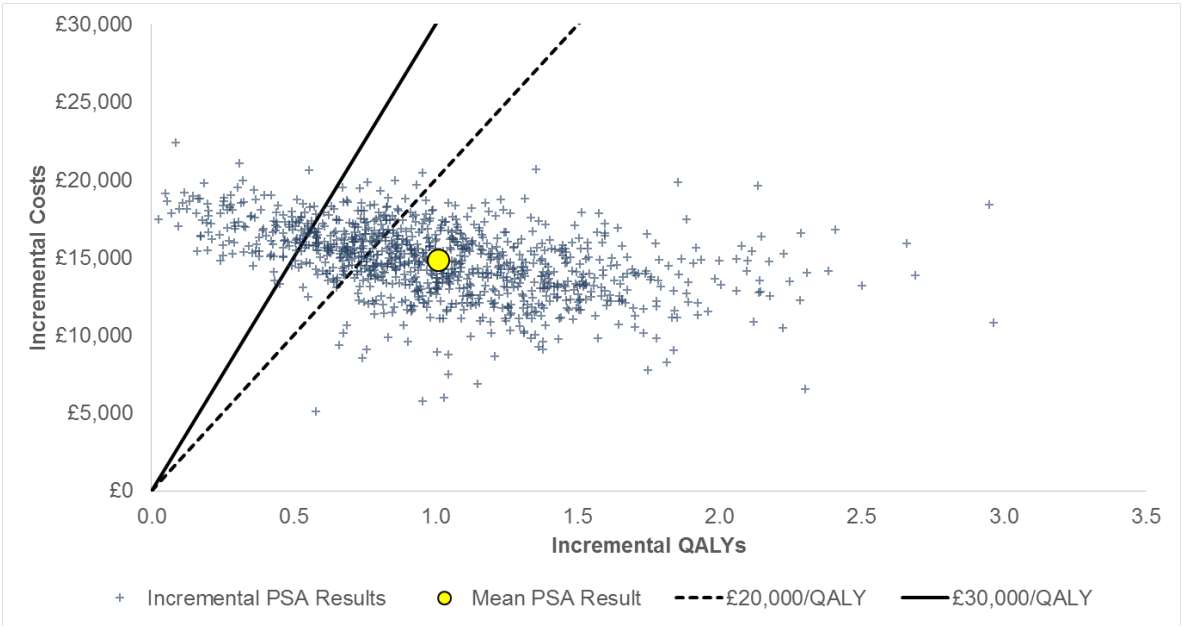


Figure 3: Results from 1,000 probabilistic model runs, 1.5% discount rate



SCENARIO ANALYSES

Various scenario analyses have been undertaken in order to quantify the impact of structural uncertainty on the ICER, listed below.

TREATMENT FAILURE AND KNEE REPLACEMENT SCENARIOS

- Assume ChondroCelect failure rate is equal to microfracture failure rate after five years – a conservative assumption to show the sensitivity of modelling to long term data
- Reduce the ChondroCelect failure rate to 3/7 (three-sevenths) of its base case value, to reflect that 4 out of 7 failures observed in TIG/ACT were due to loosening which would not occur with the more modern procedure used in current practice
- Microfracture failure rate doubled after 5 years – as heard from clinicians, there is doubt about the long term durability of microfracture
- Assume no reduction in efficacy associated with a second microfracture – a conservative assumption, that although implausible, provides a bookend for estimates
- Allow knee replacements for patients at any age, as per original analysis
- Death rate from knee replacement halved – in the revised model patients must be aged 55 or over before receiving a knee replacement, as such we suggest the NHS mean death rate is the most appropriate figure

All ICERs resulting from these scenarios remain below £30,000 per additional QALY (Table 11). Assuming that ChondroCelect has a failure rate equal to microfracture after five years – the duration over which the TTF curves are modelling the data, rather than extrapolating from data – produces an ICER of £28,749. This remains within the range typically considered to be cost-effective, despite the highly conservative efficacy assumption made.

Reducing the ChondroCelect failure rate to 3/7 times its base case value leads to a highly cost-effective ICER of £18,522.

An alternative scenario analysis where microfracture failure rates are doubled after five years, in keeping with the assumptions of the assessment group, and views of experts at the committee meeting, of microfracture faring worse over time. Here the ICER is £17,651.

These results show that despite the clinical data for ChondroCelect being limited to 5 years (a long trial by most standards), longer term estimates of efficacy are unlikely to show ChondroCelect to be cost-ineffective, and therefore further research is unlikely to change investment decisions.

As noted earlier in this response document, ChondroCelect is suitable to be considered using the lower discount rate of 1.5% per year. Assuming equivalent failure rates with the 1.5% discount rate after five years produces an ICER of £16,952.

Table 11: Scenario analysis cost-effectiveness results, 3.5% discount rate

Input	Base case assumption	Scenario analysis	Incremental Costs	Incremental QALYs	ICER
Base case model	-	-	£16,238	0.63	**£25,961**
Relative efficacy extrapolation	Failure defined by respective TTF curves	ChondroCelect failure equal to MFx after 5 years	£16,740	0.58	**£28,749**
		ChondroCelect failure rate reduced to 3/7 times base case value	£14,493	0.78	**£18,522**
		MFx failure rate doubled after 5 years	£14,994	0.85	**£17,651**
Efficacy of second microfracture	Twice as likely to fail (half as effective)	No reduction in microfracture efficacy	£16,289	0.62	**£26,369**
Role of knee replacement surgery	Allowed subject to minimum age restriction: 55 years	No minimum age limit	£14,265	0.79	**£18,079**
	Mortality rate: 1.6% then 2.5%	Knee replacement mortality rate halved	£16,217	0.61	**£26,799**
Key: ICER, incremental cost-effectiveness ratio; MFx, microfracture; QALYs, quality-adjusted life years; TTF, time to treatment failure.					

Table 12: Scenario analysis cost-effectiveness results, 1.5% discount rate

Input	Base case assumption	Scenario analysis	Incremental Costs	Incremental QALYs	ICER
Base case model	-	-	£14,749	1.00	**£14,727**
Relative efficacy extrapolation	Failure defined by respective TTF curves	ChondroCelect failure equal to MFx after 5 years	£15,556	0.92	**£16,952**
		ChondroCelect failure rate reduced to 3/7 times base case value	£11,950	1.30	**£9,200**
		MFx failure rate doubled after 5 years	£12,683	1.38	**£9,210**
Efficacy of second microfracture	Twice as likely to fail (half as effective)	No reduction in microfracture efficacy	£14,841	0.99	**£15,031**
Role of knee replacement surgery	Allowed subject to minimum age restriction: 55 years	No minimum age limit	£12,575	1.30	**£9,706**
	Mortality rate: 1.6% then 2.5%	Knee replacement mortality rate halved	£14,707	0.96	**£15,334**
Key: ICER, incremental cost-effectiveness ratio; MFx, microfracture; QALYs, quality-adjusted life years; TTF, time to treatment failure					

SUBGROUP ANALYSIS: PATIENTS WITH <3 YEARS SINCE ONSET OF SYMPTOMS

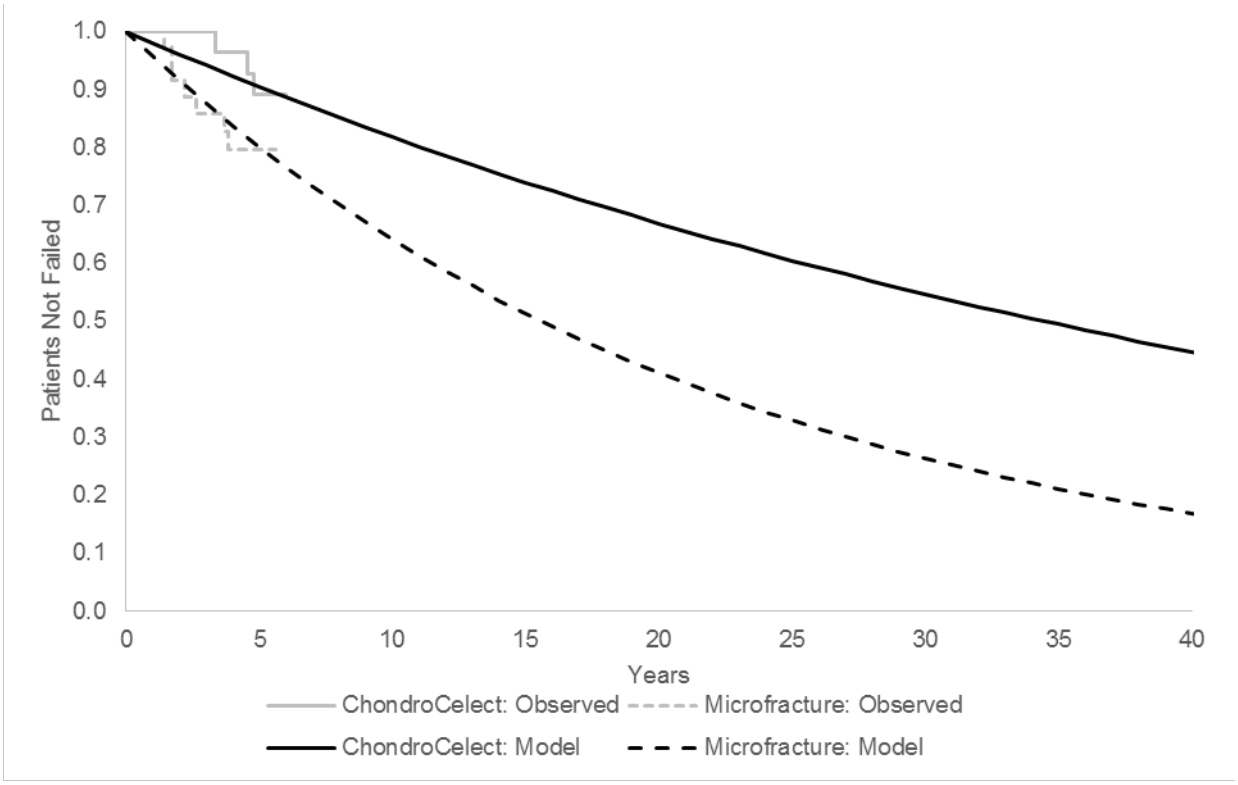
In section 5.7 of the ACD, the Committee conclude that *"there is insufficient evidence with which to identify a more favourable subgroup"*. Clinical evidence in other trials, the TIG/ACT trial, and reimbursement for ChondroCelect in other countries uses the group of patients whose onset of symptoms occurred less than 3 years prior to their intervention (n=80; 40 on the ChondroCelect arm, 40 on the microfracture arm).

The exponential models used to characterise TTF for this patient group are provided in Table 14 and Figure 4, from which a further improvement in the relative effectiveness of ChondroCelect compared to the microfracture is evident.

Table 13: Exponential survival curve parameters for TTF of patients with onset <3 years prior to intervention

Arm	Exponential coefficient	Standard error	Resulting constant failure rate
ChondroCelect	-3.905678	0.5773503	0.17% per month
Microfracture	-3.112004	0.3779645	0.37% per month

Figure 4: Exponential curves for subgroup of patients with onset <3 years prior



Applying these TTF curves in the revised model, adjusting the mean patient age at baseline to 34.1 years and proportion of female patients to 31.25% (the baseline characteristics for these patients), sees the ChondroCelect ICER fall to £19,494. Discounting at 1.5% per year, the ICER is £10,111, with ChondroCelect generating 1.25 incremental QALYs.

Table 14: Onset <3 years subgroup analysis, 3.5% discount rate

Model arm	Total			Incremental			ICER
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Microfracture	£8,484	23.07	15.80				
ChondroCelect	£23,405	23.17	16.57	£14,921	0.10	0.77	**£19,494**
Key: ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years.							

Table 15: Onset <3 years subgroup analysis, 1.5% discount rate

Model arm	Total			Incremental			ICER
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Microfracture	£12,630	33.37	22.16				
ChondroCelect	£25,314	33.58	23.41	£12,684	0.21	1.25	**£10,111**
Key: ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years.							

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Vericel's response to NICE's ACD for autologous chondrocyte implantation for repairing symptomatic articular cartilage defects of the knee

Date: 7 April 2015

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1 Comments from Vericel based on the Appraisal Committee Decision

Appraisal Committee:

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

Vericel Response:

Given the level of evidence (clinical trials and observational cohort studies), and the extent of the long-term evidence available both from randomised and observational studies, a positive recommendation for MACI/ACI treatment as first -line therapy should be allowed by the NHS.

Level of Evidence

Autologous Chondrocyte implantation (ACI) was first introduced in 1987 by Professors Lars Peterson, Mats Brittberg, Anders Lindahl from Gothenburg Sweden. Since then thousands of patients have been treated with ACI around the world. ACI has a long-standing, well-established history of consistent outcomes and high patient satisfaction. In the last ten years, ACI technology has further been evaluated in a number of randomised studies. Eleven of those studies have evaluated ACI versus another repair technique. Seven of the eleven studies showed that ACI to be superior over the other technique. [1 2 3 4 5 6 7 8 9 10 11]

Two of the randomised clinical trials, the SUMMIT trial for MACI and ChondroCelect®, are registered as Advanced Therapy Medicinal Products (ATMP) under EMA regulations, and have thus passed all requirements for evidenced-based standards for clinical outcomes. To meet EMA regulations and standards for phase 3 clinical trials, the number of patients included in the studies are determined based on the power to detect a difference in treatment between randomised treatment arms. For the SUMMIT study, given the length of follow-up and taking into account a possible 15% reduction in sample size due to early discontinuation of patients from the study, this calculation resulted in a total sample size of 144 patients (72 in each treatment arm).

The level of evidence, utilization and majority opinion amongst cartilage experts from the British Orthopaedic Society, the British Association for Surgery of the Knee (BASK) and board members of the International Cartilage Repair Society confirms the wide acceptance of ACI for the treatment of articular cartilage defects. In a consensus statement on surgical technique that was published following a consensus meeting of leading European orthopaedic surgeons specializing in cartilage repair, Steinwachs *et al* stated "Autologous chondrocyte transplantation has become an established therapy for full-thickness cartilage defects."[12] A similar article, the UK cartilage consensus paper, with more than 100 participating surgeons, is to be published in Journal of Bone and Joint Surgery (JBJS) in April, 2015. This was part of the initial assessment review.

Long-term Evidence of Effect

Multiple generations of ACI have been used for treatment of cartilage repair, ranging from cultured chondrocytes injected as a suspension under a periosteal membrane to cells seeded on or in matrices

for safer delivery. The active ingredient is the same across generations, namely the cultured chondrocytes that are programmed to produce cartilage, rendering all forms relevant when comparing outcomes. Nine studies of ACI have been published with greater than ten years of follow-up, and some studies have as long as 20 years of follow-up. These studies have shown that ACI produces a robust, durable repair tissue that allows patients to return to active and productive lives (See Table 3 for additional detailed information). There are another nine publications with 5 to 9 years of follow-up. The majority of these have been academic cohort studies and support the findings that ACI is a durable repair (Table 1). While the types of studies vary, including academic randomised and cohort studies, the pattern of data show repeatability in the durability of efficacy across studies.

Given the level and extent of the shorter-term (2-year) and longer-term (up to 20 years) evidence available both from randomized clinical trials and observational studies, and the fact that ACI was found to be cost-effective under most assumptions (see additional details in Section 7), a positive recommendation for MACI/ACI technology should be allowed for use on the NHS.

Our recommendation to the committee is *to allow the use of ACI, following accepted treatment algorithms and EMA guidelines, to allow the physician to decide the best course of treatment, especially for those cases involving higher complexity where there are few treatment options.*

2 Clinical Comparators and Evidence of Effect

2.1 Microfracture as a comparator

Appraisal Committee:

"Microfracture involves drilling small holes through the bone under the damaged cartilage to allow bone marrow cells to fill the damaged area and to differentiate into chondrocytes."

Vericel Response:

Microfracture is not considered a drilling procedure, but is a perforation of the subchondral bone plate to reach intracortical vessels. The resulting bleeding from penetrating the subchondral plate develops into a blood clot that functions as a scaffold to attract cells from the bone marrow. Such cells could be mesenchymal stem cells (MSC) that may go into a chondrogeneic lineage producing a fibrocartilaginous tissue repair. However, they are not pure chondrocytes and there is no evidence to show the actual number of stem cells involved in this repair process. [13]

Appraisal Committee:

"Microfracture is normally used for lesion sizes of less than 13 cm^2".

Vericel Response:

Lesion Size Appropriate for Microfracture Treatment

The current literature references on microfracture is consistent with microfracture used only for smaller lesions. Specifically, using microfracture in larger lesions damages the subchondral bone, which causes a change the architecture of the cartilage bone junction causing it to become much stiffer and increasing stress and shear forces at the cartilage-bone interface with larger lesions. [14] [15] [16] *[17]*

Therefore, in patients with cartilage lesions >4cm^2 there are few treatment options, and this is where ACI has been found to be effective (see also Lesion size ACI vs Microfracture, below).

The Mithoefer systematic review[18], describes the lesion size in which microfracture performs the best, namely in smaller lesions (< 2-3cm^2) that are well contained, shouldered edges, not beveled to help protect against the opposing forces. Younger patients (<45 years of age), with a BMI <30 and a duration of symptoms of <12 months are also key predictors. In addition it is important to note that the result of the procedure is highly dependent on the compliance with rehabilitation protocol. Mithoefer's review suggests that microfracture is not preferred for larger defects due to it creates fibrocartilage repair tissue, the wear characteristics of the repair tissue are unknown over time and the fill rate can be unpredictable.

A small well-shouldered chondral defect prevents damage to the opposing surface, because the shoulders of the defect supports the subchondral bone. This is where a fibrocartilage repair tissue works with lesions between 2 to 3 cm^2. For larger lesions, there is an overload on the cartilage rims and there are forces working against the opposing subchondral bone. In this situation, a more durable repair tissue is needed with mechanical properties closer to hyaline tissue. Peterson et al, 2002, examined the biomechanical properties with long-term follow-up.[19]

Another comparator that was mentioned in the assessment report, is mosaicplasty. This procedure is mostly used for small areas of damage (less than 2 cm^2) and indicated mainly for osteochondral lesions and defects where 1-2 plugs can sufficiently fill the symptomatic defect.

Lesion Size ACI vs Microfracture

It is clear that ACI is suitable for a wider range of lesions sizes than microfracture. This was reported in a publication of the results of SUMMIT[20], where a range of 3 to 20 cm^2 was included, and also in the European Public Assessment Report (EPAR) of MACI where the EMA concluded:

> "the potential effect of lesion size was considered important by the Committees. In a subgroup analysis of the group with larger lesions (> 4 cm^2) in the pivotal study, MACI was superior to MFX (KOOS response rates 97% vs. 77%), while a positive trend was seen for the individual components of the co-primary efficacy parameter for both pain and function. However, in the group with smaller lesions (< 4 cm^2), where microfracture is considered the treatment of choice of choice, there was also a benefit for MACI (KOOS response rates (78% vs. 61%). Overall, the

Committees concluded that the benefit of MACI is not restricted to a particular size of lesion and can be used for lesions from 3 to 20 cm^2." [21]

This is further confirmed by the systematic reviews by Oussedik[26] that also concludes that in lesions greater than 4 cm^2, ACI has been shown to be more effective than microfracture.

2.2 Clinical Effectiveness Evidence

2.2.1 SUMMIT Trial

2.2.1.1 Trial Size

To meet EMA regulations and standards for phase 3 clinical trials, the number of patients included in the studies are determined based on the power to detect a difference in treatment between randomised treatment arms. For the SUMMIT study, given the length of follow-up and taking into account a possible 15% reduction of patients due to early discontinuation from the study, this calculation resulted in a total sample size of 144 patients (72 in each treatment arm).

2.2.1.2 Primary Endpoint (co-primary KOOS pain and function)

The SUMMIT trial was based on superiority on the Knee injury and Osteoarthritis Outcome Score (KOOS). The Appraisal Committee concluded that the KOOS is the most appropriate score to assess clinical effectiveness. KOOS is a validated patient outcome tool designed to assess the patient's opinion of his/her knee and associated problems. The sensitivity of the KOOS scores has been validated and reliably reports changes in the five subscales of overall knee health. A 10-point improvement on KOOS represents a clinically important difference in effect of treatment.

While KOOS is the preferred outcome measure, the Lysholm, Tegner and Cincinnati scores are also considered reasonable and reliable measures of pain and function and most importantly allow for intra-study comparisons from a historical perspective.

2.2.1.3 Study Design and Results

The SUMMIT trial is the only cartilage trial designed to demonstrate Superiority of Matrix-induced autologous chondrocyte implant versus Microfracture in patients with symptomatic articular cartilage defects in the knee. SUMMIT represents the largest, most rigorous GCP, randomized, controlled trial of cartilage repair to date. It was designed to meet the new ATMP regulations for EMA.

To date, the SUMMIT trial is viewed as one of the most comprehensive trial in cartilage repair field based upon its unique design, as is evident from a statement by the Committee for Medicinal Products for Human Use (CHMP). They noted that the approval of MACI was based on

"the robust clinical data from a prospective study showing clinically relevant effects and confirming an acceptable and manageable safety profile, the Committees concluded that the benefit/risk balance of MACI for the repair of symptomatic, full-thickness cartilage defects of the knee is positive. The clinical study data was further supported by information from published literature as MACI has been available in some European countries since 1998 in accordance with national legislation before coming under the

new legal framework for advanced therapies. MACI has completed all the requirements for licensing as the first advanced-therapy medicine to be combined with a medical device." [21]

Factors that led to this conclusion include:

- Sites were trained in standardized microfracture and MACI implant surgical and rehab procedures to minimize investigator variability
- Validated clinical outcomes; Histology (ICRS II) scores used.
- MRI to assess defect fill
- Response rate based on KOOS pain and function
- Comprehensive patient follow-up
- High number of patients completing the study (intent-to-treat population)
- 70/72 MACI patients, and 67/72 microfracture patients completed the trial
- 5-year extension study in progress for further follow up

SUMMIT screened 189 patients, and 144 patients were randomised (72 patients in each study arm). At Week 104 (Year 2), the improvement in the MACI group compared with microfracture with regards to the co-primary endpoint of KOOS pain and function (SRA) was clinically and statistically significant ($p = 0.001$. The partial correlation (p-value) for the primary analysis was 0.746 ($p < 0.001$) indicating a high strength of dependence of the co-primary endpoints.

Secondary endpoints also demonstrated statistically significant differences favoring MACI compared to microfracture at Week 104; these included activities of daily living ($p < 0.001$), knee-related quality of life ($p = 0.029$), other symptoms ($p < 0.001$), and modified Cincinnati knee rating system overall score ($p = 0.002$).

The primary efficacy endpoint was corroborated by other validated patient-reported outcome measures included in the study (SF-12 physical health score, and IKDC Subjective Knee Evaluation). In addition, significantly more patients treated with MACI (87.5%) met the responder analysis criteria (defined as improvement from Baseline to Week 104 of at least 10 points in both KOOS Pain and Function [SRA]) than patients treated with microfracture (68.06%) ($p = 0.016$).

The planned analyses for treatment failure rates and treatment group differences were not possible due to the small number of per protocol treatment failure cases. Only 5 patients (1 MACI and 4 microfracture) were confirmed as treatment failures by the Independent Treatment Failure Evaluation Committee.

2.2.2 Additional ACI Evidence (Carticel®)

In the US, the FDA required two post-approval studies for Carticel®, autologous chondrocytes delivered as a suspension and secured by periosteal flap. As a consequence of the post-approval requirement, the Registry-based study and a phase IV study, the STAR study, were conducted. These studies were designed to collect multicenter assessment of outcomes in the general orthopaedic practice. The strengths of the Registry-based and STAR study were that both involved prospective data collection, had an independent oversight board, used *a priori* cohort identification and analysis plans, involved a HIPAA

compliant database, and met AHRQ guidelines for high quality registry design. Based upon the successful outcome of these studies, ACI was approved by the FDA in 2006 and 85% of the insurance companies have medical policy to cover ACI for full-thickness symptomatic cartilage defects.

The MACI STAR, and Registry-based studies used the same active ingredient, autologous chondrocytes, manufactured in the same facility. Although the designs of the 3 ACI studies (SUMMIT, STAR, and Registry-based) were different (ie, randomized clinical trial, open-label cohort, and registry-based observational, respectively), efficacy results of within-patient change from baseline status following autologous cell treatment showed a similar pattern on KOOS (SUMMIT and STAR; not collected in Registry-based) and modified Cincinnati scores supporting the efficacy of the autologous cells to repair the cartilage defect.

Descriptions of the Carticel® studies are provided, below.

2.2.2.1 Registry-based study

The Registry-based study was an open-label, prospective, multicenter study within-patient evaluation of patients with articular cartilage defects of the knee who had an inadequate response to a prior non-ACI intervention.[22] Ninety-seven patients with an average lesion size of 4.9cm^2 were followed for a period of up to five years. A total of 70% of patients demonstrated both a statistically and clinically significant 4.1 point improvement with the Modified Cincinnati Rating Scale.[23] A 2-point change on this scale represents a clinically meaningful difference, and thus this was largely surpassed in the Registry study.

2.2.2.2 STAR study

The STAR study was a phase IV, open-label, prospective, multicenter (29 centres in total), within-patient evaluation study of patients with articular cartilage defects of the knee who had an inadequate response to a non-ACI prior surgical treatment and then subsequently received ACI. [24] The objective of the STAR study was to confirm durability and effectiveness of ACI for the labeled FDA indication.[*] This study included a challenging patient population with large lesions, severe symptoms at baseline and having failed prior treatment(s). The sample size was 154 patients and the study had a length of follow-up of four years, establishing the STAR study as the largest cartilage repair study in the United States.

All primary and secondary endpoints were met. ACI demonstrated sustained improvements in knee function as early as 6 months and out to 4 years (as measured by KOOS). A total of 77% of evaluable

[*] US FDA-approved indication for Carticel® (autologous cultured chondrocytes) is an autologous cellular product indicated for the repair of symptomatic cartilage defects of the femoral condyle (medial, lateral or trochlea), caused by acute or repetitive trauma, in patients who have had an inadequate response to a prior arthroscopic or other surgical repair procedure (e.g., debridement, microfracture, drilling/abrasion arthroplasty, or osteochondral allograft/autograft). Carticel should only be used in conjunction with debridement, placement of a periosteal flap and rehabilitation. The independent contributions of the autologous cultured chondrocytes and other components of the therapy to outcome are unknown. Carticel is not indicated for the treatment of cartilage damage associated with generalized osteoarthritis. Carticel is not recommended for patients with total meniscectomy unless surgically reconstructed prior to or concurrent with Carticel implantation.

patients reported a follow-up score of “good” to “excellent.” Of all evaluable patients, 50% “very good” or “excellent” results, indicating few or no limitations participating in sports.

The safety results of STAR were consistent with the known ACI safety profile. Patients in STAR presented with many clinical challenges and, as expected, subsequent surgical procedures (SSPs) were reported. A total of 49% (N=76) of patients underwent an SSP irrespective of relationship to ACI. Of the patients who underwent an SSP, 83% (63/76) underwent an arthroscopy or manipulation under anesthesia only. Lysis of adhesions was the most frequent surgical intervention performed in the first 6 months. Cartilage debridement was the most frequently performed intervention after 6 months. The most common serious adverse events (≥5% of patients), derived from STAR , include arthrofibrosis/joint adhesions, graft overgrowth, chondromalacia or chondrosis, cartilage injury, graft complication, meniscal lesion, graft delamination, and osteoarthritis. Subsequent surgical procedures were not indicative of treatment failure in STAR. Of the patients who required an SSP, 61% (46/76) did not meet the study definition of treatment failure (e.g., graft delamination or surgical procedure violating the subchondral bone).

2.2.2.3 Systematic Reviews and Meta-Analyses

There are several sources of information involving either MACI or ACI.

A meta-analysis by Negrin, which set out to test whether ACI was superior to microfracture, concluded that when taking into consideration only second and third generation ACIs, differences with microfracture were significant though converging over time. This was based on a review of six studies involving a total of 399 patients aged between 16 and 60 years with lesion sizes between 1 and 10 cm^2.[25]

A systematic literature review by Ossendik indicated that ACI is more effective than microfracture, especially in lesions larger than 4 cm^2. [26]

An indirect comparison of MACI versus ACI and MACI versus mosaicplasty was undertaken for an MSAC submission for MACI in Australia in January 2013. Overall, the analyses showed no significant difference between ACI and MACI in the likelihood of achieving a response to treatment. [27]

2.2.2.4 Long-term Follow-up Data

There is a substantial amount of data (approximately 1,000 patients reported in the publications) on longer term efficacy as shown in Table 1. These data show that at 5 years 10% of patients reported a failure with MACI. These 5-year failure rates are lower than those reported in the Appraisal Committee’s Report, which used failure rates of 13.1% at three years.

A consistent finding with both randomized controlled trials and the 5-year studies from Ebert[28] and Marlovits[29] was an early response that was maintained over time.

Table 1. Overview of long-term MACI data

Author Journal	Number of Patients (average age)	Follow-up Mean yrs	Ave lesion size	Failure Rate	Clinical Outcomes	Patient Satisfaction
Ebert 2012[28]	41 (38.5 yoa)	5 years	3.0cm^2	10%	Sign improvement at 5 years KOOS, SF-36 and 6 minute walk test 67% fill rate at 5 years 86% able to resume all daily living skills 73% able to return to sports	98%
Marlovits 2012[29]	21 (35.2yoa)	5 years	5.1cm^2	10%	Sign improvement of KOOS at 1 yr; maintained for 5 yrs in > 90% IKDC- 30.1 – 74.3 MCS: 38.1 – 79.6 Tegner 1.8-4.3 83% complete fill- 47% BME at 5yrs	90%
Nawaz 2014[30]	827 308-ACI 519-MACI	5-10yrs	4.09cm^2	30%	78% Graft Survival at 5 years 51% at 10yrs Stanmore 2.78 – 1.70 VAS 5.95-3.56 MCS: 46.9 – 66.7 Patients factors identified as not doing well: Degenerative changes prior to implantation & >2 previous procedures Key Points: Patients with degenerative changes and slight varus did not receive an HTO	NA
Brix 2014[31]	53pts	9.7yrs (2-12yrs)	4.4cm^2	22.6%	IKDC pre-40.4 post 74.7 at 10yrs Stat sign increase in all scores at all time points (Lysholm, MCS)	90%

HTO = high tibial osteotomy

There are an additional nine studies reporting long-term data for earlier generations of ACI. The Appraisal Committee report indicated that they felt these earlier generations of ACI were of less value for this MTA. However, comparability data have shown that the active compound (cultured chondrocytes) in MACI is essentially the same as the first generation products. MACI was developed as a means of delivering the cells in a more efficient and safer method when compared to the first generation. Therefore, these long-term data from the first generations should not be considered obsolete, but rather as establishing a pattern of the long-term durability.

ACI has a well-established history. From studies using the first generation techniques, long-term follow-up has been published in over ten publications. These studies provide long-term efficacy in

864 patients with more than ten years of follow-up, and 411 patients with between five and 10 years of follow-up.

Table 2 below shows these nine studies of earlier ACI versions, each reporting similar failure rates, approximately 25%. This is similar to 10-year results reported with the newer versions of ACI. However at shorter time frames, ie, five years, failure rates are for third generation MACI are much lower, namely 10%. A consistent finding with the long-term results was a high patient satisfaction rate, even at 20 years of follow-up.

Table 2. Overview of long-term data earlier generation ACI data

Author Journal	Number of Patients	Follow-up Mean yrs	Size of Lesions	Failure Rate	Clinical Outcomes	Patient Satisfaction
Peterson 2010[32]	224	12.8 yrs	5.3cm^2	26%	74% of patients reported improved over initial results: Lysholm, Tegner and Peterson-Brittberg scale all improved Normal aging process and changing social factors played a role in the decline	92%
Biant 2014[33]	104	7.8 yrs	4.7cm^2	26%	88% reported good to excellent VAS scores decreased by 8 pts	98%
Mosely 2010[34]	72	9.2 yrs	5.2cm^2	17%	87% maintained or improved from five year assessment. 5 to 10 years sustained improvement 69% maintained >3pt On Mod Cin Rating Scale	80%
Niemeyer 2013[35]	86	10.9 yrs	6.5cm^2	26%	Lysholm- 42-72 IKDC – 74 VAS- x-1.9	77%
Minas 2013[36]	210	12 yrs	8.4cm^2	26% 9% TKA 13% Biological Failures	78% Good to Excellent Statistically Significant- • Mod Cincinnati Score • WOMAC • KSS • SF-36	87% Sustained pain relief Graft Survival At 15 years 88% -HTO 60%-Without
Bentley 2012[37]	100 pts	10yrs	Avg Size-4.66cm2 4.6cm2-ACI 3.9cm2 -	17%	ACI better scores Modified Cin Scores and Bentley Scores ACI 73% GE 10yrs MP 60% GE 10yrs Graft Failure: 10/58 (17%) ACI 22/42 (55%) Mosaicplasty	

			MP		All Mosaicplasty patella lesions failed	
Martinicic 2014[38]	33 pts	10 yrs	Avg 4.3cm2	7%	10 yrs- IKDC – 15 Normal, 11 near normal, 5 abnormal and 2 severely abnormal 45% of the pts showed radiolographic changes	
Moradi 2012[39]	23 pts	Mean 9.9yrs (7-14)	4.3cm2 (2-12cm2)	8.7%	78.3% Good to excellent results Small deterioration noticed at final evaluation, but still significant over pre-value. MRI findings confirmed defect filling in 52.3% of the lesions regardless of size	73.1%
Pelissier 2014[40]	12pts	10yrs			MRI- 9 of 12 pts >50% fill of defect at 10 yrs Sustainedimproved functional outcomes for 10 yrs	

A systematic review by Harris of failures and complications after ACI, reported that failure rates were higher with first generation ACI-P than with second-generation ACI-C and thus confirms the observations in the studies mentioned above.[41]

With regards to the Assessment Group's review of additional long-term studies, the information on the Minas paper was interpreted incorrectly: This paper was cited by the Committee as not supporting ACI over microfracture for the treatment of larger lesions. The focus of the paper was examining the damage MFX causes on the subchondral bone and in case of advanced bony pathology, ACI outcomes can be affected. If the chondral lesions without significant degenerative changes to the underlying bone are considered, the Minas paper supports the long-term efficacy of ACI.[42]

2.2.3 Need for additional research

The Committee identified a need for additional research. This is surprising as not only is there substantial evidence available, NICE issued positive recommendations on various technologies with much less longer term evidence than is available for ACI. One such precedent is IPG 456[43] where suture-less aortic valve replacement was allowed as part of standard NHS procedures based on only short-term evidence (ie a case series of 208 patients and a study with one-year follow-up, while there was some real-world data on one to four year follow-up).

Another example is TA152 (Drug-eluting stents for the treatment of coronary artery disease2008), which seems to be based on three-year data only, while this is an invasive treatment that can have serious side-effects, yet was approved without the need for further research. [44]

Finally there is the example of the anti-TNFs in psoriatic arthritis. Here the three drugs assessed: etanercept, infliximab and adalimumab, only had very limited data on which the assessment was based, namely 24 weeks, 50 weeks and 24 weeks with 12 weeks follow up, respectively. Again this concerns a

systemic treatment which carries the risk of (serious) adverse events and had uncertainty about long term efficacy, yet this treatment was allowed without the restriction to research. [45] Similar levels of evidence were deemed sufficient in rheumatoid arthritis.

Therefore, given the availability of much longer-term data as described above, Vericel is not convinced that additional data are needed on ACI.

3 Evidence for Potential Subgroups

3.1 First-line

Vericel supports the use of ACI as a first-line treatment. In the SUMMIT study, approximately two-thirds of patients did not have a prior therapy, and results were clinically and statistically significant in the full analysis set.

In addition, in the approximately one-third of patients who did have a prior therapy, the effect of MACI treatment was still significantly more improved at Year 2 compared with microfracture treatment.

Table 3. KOOS Pain and Function in SUMMIT patients at 2 years

		Treatment Group and Patient Population			
		SUMMIT Full analysis set		**SUMMIT prior surgical procedure**	
	KOOS	**MACI (N=72)**	**Microfracture (N=70)**	**MACI (N=22)**	**Microfracture (N=25)**
Pain					
Baseline	Mean (SD)	37.00 (13.52)	35.45 (12.09)	39.27 (14.09)	35.11 (10.23)
Year 2	Mean (SD)	82.45 (16.18)	70.85 (24.22)	81.19 (17.06)	59.11 (22.84)
Change from Baseline	Mean (SD)	**45.45 (21.08)**	**35.23 (23.91)**	**41.92 (22.07)**	**24.00 (19.88)**
Function, Sports and Recreational Activities					
Baseline	Mean (SD)	14.86 (14.68)	12.57 (16.67)	16.14 (13.45)	9.60 (10.30)
Year 2	Mean (SD)	60.90 (27.84)	48.71 (30.33)	59.55 (30.59)	36.80 (27.87)
Change from Baseline	Mean (SD)	**46.04 (28.35)**	**35.83 (31.63)**	**43.41 (29.66)**	**27.20 (27.16)**

KOOS=Knee Injury and Osteoarthritis Outcome Score; FAS=full analysis set; n=number of patients in a treatment group; SD=standard deviation; SRA=Sports and Recreational Activities.; LOCF method used to account for missing data for both Summit analyses.

3.2 Lesion size (>4cm^2)

From the published evidence it is clear that the defect size, and especially lesions >4 cm^2, is the primary factor predictive of better outcomes when ACI was compared to other techniques (such as MFX).[41] This is further substantiated by published literature which shows that microfracture treatment did worse in

lesions than 2cm^2. In a direct comparison study of microfracture vs ACI, Knutsen *et al* found in patients with lesions <4 cm2, there was no difference between the two treatments. But in lesions greater than 4 cm^2, ACI performed better at 2 and 5 years.[46]

3.3 Need for additional research

The Appraisal Committee identified a need for additional research. Vericel respectfully disagrees with this position given the large volume of data that exists on this topic, including randomized, observation studies and academic cohort studies from around the world.

4 Cost-effectiveness/ efficacy values / second repair/number of people having a TKR/Costs

From the meeting is seems clear that the Committee is not fully convinced of the validity of the Assessment Groups approach and design of the cost-effectiveness model. Vericel shares some of these reservations (eg the utility values from the SUMMIT trial should have been used but were not identified from the systematic review, available longer term data were not used); however, the results were robust to most of the assumptions. All but a few of the sensitivity analyses resulted in ICERs below NICE's threshold.

Although it is agreed that there are several uncertainties, for example about practice patterns, several of these could have been explored in more detail through the modelling, in order to better understand their significance. The Committee could have asked for more modelling to be done before deciding that more research is required.

5 Utility data for ICER

The systematic literature review of the Assessment Group failed to identify the abstract presented at ISPOR of the quality of life data collected alongside the SUMMIT trial. The main publication includes baseline and two-year results using the EQ-5D's visual analogue scale (VAS), (which is not the preferred method by NICE. However, in an abstract presented to the 16th European ISPOR Congress, utility values were presented using the EQ-5D questionnaire and the UK tariff.[47] As the SUMMIT quality of life data were obtained directly from patients using the EQ-5D, while the Gerlier data used in the model were from an older study, using the SF-36 using a not-described transformation method, the SUMMIT utilities, given that they were available in public domain, should have been used.

Results were available for SUMMIT patients at 2 years. The mean utility score for all patients (n=142) at baseline was 0.481±0.296. Responders (n=111) had an improvement in mean utility score from baseline of 0.352 (0.833-0.481) compared with 0.033 for non-responders (n=29; 0.514-0.481) at year 2. Significantly more patients treated with MACI responded to treatment than with MFX (87.5% vs. 68.1%, respectively; p=0.016), resulting in an incremental QALY gain of 0.11 for MACI compared with MFX over 2 years, which is generally viewed by NICE as a relevant increase. These data show that:

- At baseline patients have much worse QoL then assumed in the model ie 0.481 vs 0.654
- Responders have a better QoL than in the model 0.833 vs 0.817

- Non-responders have a worse QoL than in the model 0.514 vs 0.654

Overall the use of these data in the model would have led to a higher increase in QoL for ACI as compared to MFX and a consequent lowering of the ICER.

6 Time horizon

Vericel is in agreement with the Committee that the appropriate time horizon of the cost-effectiveness model is lifetime, as changes in mobility affect a person for the remainder of their life. However, we believe that, given the follow-up data presented above it is possible to demonstrate the cost-effectiveness of MACI without lifetime data, given that the costs of the intervention are at the time of culturing and treatment, and does not involve continuous treatment.

7 Innovation

Vericel agrees with the Committee that MACI and other ACIs are technically innovative but disagrees with the Committee that ACIs are not innovative in terms of their benefits to patients. Cultured Autologous Chondrocytes should be looked upon as the product that has progressed over time to become safer and more efficient. (M)ACI has had a large societal impact on cartilage (repair) field since 1994. It represents the safest delivery method of providing patients with autologous chondrocyte implantation. The active compound remains the cultured chondrocytes, which provide the durable repair tissue regardless of which generation of delivery is used. Nine Papers with 10 to 20 year follow-up confirm the efficacy, safety and patient satisfaction:

- 72 to 85% deemed the procedure Good to Excellent
- Average Time to Return to full activity 18 Months (range 12-36mths)
- 85% Patient Satisfaction
- 80% Patients would have surgery again

Therefore Vericel maintains that (M)ACI represents an important innovation to patients. Also, MACI is associated with an improvement on the EQ-5D of more than 0.1, which is normally considered to be an important improvement.

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POSITION STATEMENT BY BASK ON THE NICE APPRAISAL CONSULTATION DOCUMENT ON AUTOLOGOUS CHONDROCYTE IMPLANTATION 2015

26 MARCH 2015

With regard to your Appraisal Consultation Document(ACD) on the MTA (Multiple Technology Appraisal) of Autologous Chondrocyte Implantation (ACI). The British Association for Surgery of the Knee (BASK) would like to respond on behalf of its members and patients. In anticipation of this ACD, BASK discussed ACI in depth at our annual congress in Telford on 10-11th March 2015. The discussion included presentations, open debate, audience voting and an agreement on the position of the BASK with regard to ACI, its evidence base and clinical merit.

The conclusion that "Autologous chondrocyte implantation is recommended only in research for repairing symptomatic articular cartilage defects of the knee. Research should include clinical trials and observational studies designed to measure the long-term benefits of autologous chondrocyte implantation" is inconsistent with the evidence already available and has severely detrimental consequences for patients. BASK members note that the committee has misinterpreted the literature and the clinicians view of this technology.

BASK would like to contribute the following points to the appraisal:

1. The conclusions of the committee do not appear to be consistent with the evidence available. The committee appear to based their appraisal on the trials set up in response to the 2005 Appraisal and changes in EU licensing, which of course will only have short to mid-term evidence. The committee have interpreted this as a 'lack to long-term data'. There are over 1000 papers in the literature on ACI, including three long-term cohort studies with data on patients over 10 years. These seem to have been ignored by the committee in its conclusions. (see below)

2. Warwick Evidence (commissioned by the HTA programme) concluded that ACI showed a clear benefit over microfracture and mosaicplasty and there was evidence for its use as first-line therapy in appropriate patients. The committee seems to have misinterpreted this evidence and stated that the AG group considered the results of their reviews to be inconclusive on the effectiveness of ACI compared to microfracture.

3. The conclusion of AG is very similar to that of the UK Cartilage Consensus Paper, which is due for publication shortly and has close to 100 signatories of clinicians undertaking care of patients with articular cartilage injury. BASK considers that this is the majority view of experts in this area based on the evidence. BASK also believe that the committee has over-emphasised the views of a single invited expert (who rarely perfoms ACI) whose views do not reflect the majority on the effectiveness of ACI.
4. Warwick Evidence was commissioned by the HTA programme on behalf of the Dept of Health to produce an economic modelling of ACI, which found it to be a cost-effective therapy even at the 'list price' (which none of our members actually pay in the NHS due to procurement discounts). We understand that this economic modelling has itself been independently reviewed and found to be of very high scientific quality. Unfortunately the committee has not accepted this evidence.

5. The 'methodological limitations' and criticisms of the RCTs and available studies are used as a basis by the committee to suggest that further research is required. The ACD also refers to "3 small studies". The Genzyme and Tigenix studies were both sufficiently powered to show a difference, and these were large surgical

studies. The issues raised with regard to the methodology are actually inherent to this particular clinical situation and cannot be improved. Further research as suggested would not address these issues, are not possible, and would not provide additional evidence. Furthermore some suggestions by the committee for further research are likely to be unethical. The trials have been assessed using criteria not achievable in surgical trials on this population. Allocation concealment is not possible if one treatment requires a single operation and another requires two operations. Blinding of the surgeon is clearly impossible. Variations in previous treatment are inherent to this population, and reflect the population who would present requiring this surgery. The inclusion criteria for the Chondroselect and MACI RCTs are considered narrow enough to obtain comparable data between the groups and broad enough to include patients who would benefit. Stricter inclusion criteria would render the results applicable to only a very small percentage of patients who might actually present in the clinic. This in itself would be a methodological flaw.

6. With regard to committee concerns about which outcome questionnaires were used, we would comment as follows. BASK agrees that the questionnaires used in early studies were also those used to assess other soft-tissue knee problems and the response to surgery. Although the questionnaires used have evolved over time, they were consistent within studies, and often between studies. Although used for other pathology, all the questionnaires have pain and function reporting which are markers of treatment success or failure in ACI patients. Studies should not be discounted on this issue, and the committee appears to have given this matter too much emphasis in their evaluation of data.

7. With reference to section 5.4. "The Committee heard that the clinical experts differed with respect to how effective they perceived ACI to be compared with microfracture. The committee heard that this may in part reflect a clinician's experience and preference. When asked to judge the clinical effectiveness of ACI, clinical experts stated that there was some evidence to show that ACI is clinically effective, but also stated that this evidence was not definitive. They also stated that, although ACI, microfracture, and mosaicplasty were probably clinically effective, evidence was lacking for the natural history of lesions treated by debridement and lavage". BASK disagree. This is absolutely not the clinical situation or the view of the majority of knee surgeons. The views of one "clinician expert", without sound evidence seem to carry more weight than would be merited. ACI has a very strong evidence base for safety and efficacy in worldwide clinical practise, it is not merely dependent on one doctor's personal experience. We would consider the evidence definitive. The natural history of untreated large articular cartilage lesions is osteoarthritis. This is beyond doubt. Two of the clinical experts present confirmed this. It is possible that a view that a single clinician "expert" who gave written and verbal opinions has skewed the committee into believing there was vast difference of opinion within the orthopaedic community In fact there is not. Based on the views expressed at the recent BASK congress and those signing the UK Cartilage Consensus statements the majority view of those who undertake cartilage repair surgery is that ACI is safe, effective, and superior to comparators in many situations.

8. With regard to the AG evaluation of the effectiveness of ACI, and the committee concern that the AG favoured inappropriately. The AG view of this is justified by reference to the long-term cohort studies and the RCT of ACI vs Mosaicplasty at 10 years by Bentley 2012, which demonstrate enduring results with ACI even in unfavourable large multi-operated knees. Other papers which support our view are:
   Minas T et al Clin Orthop Relat Res. 2014 Jan;472(1):41-51.
   Biant LC et al Am J Sports Med. 2014;42(9):2178-83.
   Peterson L et al Am J Sports Med. 2010 Jun;38(6):1117-24.

9. The recommendations of the committee for further research is misguided with regard to this appraisal. Suggesting that an RCT should be done against physiotherapy, sham surgery or debridement alone implies a misunderstanding of the indication for surgery in the first place. All patients considered for ACI will have had physiotherapy and failure of conservative treatment, and nearly all will have had an arthroscopic debridement and lavage and further physiotherapy before ACI is considered. We believe, once again that, the unsubstantiated opinion of one clinician has been weighted too heavily.

   An RCT against physio alone is not reasonable as all these patients have already failed conservative treatment. An RCT against debridement alone is not reasonable as most of the patients will have already failed this before ACI would be considered. An RCT against sham surgery could be deemed unethical, as most patients will already have had a failure of debridement.

   Other considerations for the Committee are important for patients:

   1. In large lesions, ACI is the ONLY proven therapy that is effective. Even those who advocate microfracture acknowledge that microfracture should not be performed in lesions over 2cm. Furthermore, doing ACI as second line after failed microfracture renders the patient with a less favourable outcome than if ACI done first. NICE is about to deny NHS patients the only effective treatment for their pathology.

   2. No further research is likely to be funded by industry or grant-awarding bodies, as this is established treatment that has been in practice for over 25 years. Good research exists, funding of further research will not be forthcoming. NICE Committee interpretation of available literature exhibits a misunderstanding of the clinical situation.

   3. NICE research suggestions are entirely inappropriate to our patients.

   4. Suggesting ACI only in the context of further research is not a safe or pragmatic compromise option. It will effectively kill the technique in the UK and significantly disadvantage our patients. Moreover, it will set back healthcare in regenerative orthopaedics back 25 years instead of facilitating responsible innovation.

      BASK members believe that ACI should be publically funded on the NHS for appropriate patients who have failed conservative treatment. Collection of outcome data could be mandated. The International Cartilage Repair Society has a registry in progress. Centralising services in a small number of centres regionally is sensible and reduces overall cost.

POSITION STATEMENT BY BRITISH ORTHOPAEDIC ASSOCIATION ON THE NICE APPRAISALCONSULTATION DOCUMENT ON AUTOLOGOUS CHONDROCYTE IMPLANTATION (ACI) 2015

30 MARCH 2015

The conclusion reached in the Appraisal Consultation Document (ACD) on the Multiple Technology Appraisal of ACI is flawed and detrimental to good patient care for a number of reasons.

Since the last appraisal in 2005 a number of trials which had already started before 2005 have now provided the evidence for the efficacy of ACI as a treatment for isolated chondral defects of the knee. Not only have they reported the success of this methodology but also the cost effectiveness.

The evidence from Warwick has shown what we as clinicians already know, namely that ACI produces superior results for patients in terms of pain relief when compared to microfracture and mosaicplasty not only in the short-term but also into the medium to long-term. It has been suggested that the review of the literature is inconclusive but this is not the case. The literature for ACI is more compelling and better evidenced than microfracture especially for the larger defects. There are over 1000 relevant papers in the literature and long-term studies with patient data in excess of 10 years. Further the efficacy of microfracture declines after 5 years.

ACI works and is cost effective and whilst we accept that there is more work to be done in this area to define further the patients who gain the most from this technology, it would not be in patients best interests to deny them this treatment pathway when appropriate.

We would recommend that NICE supports this treatment and it is provided through NHS funding. We would recommend and support that all patients continue to be placed into observational studies and the availability of this treatment pathway be restricted to centres who use this technology in at least 50 patients per annum. Where it is felt appropriate for patients to receive ACI, after informed consent and appropriate discussion, the treatment costs must be met by the relevant CCG. Failure to allow appropriate patients access to this technology through the NHS funding route will condemn them to a life of on-going pain and progressive joint degeneration, leading to early joint replacement and the need for expensive revision surgery. The National Clinical Reference Group for Specialist Orthopaedics have already looked into this technology and support its use.

The British Orthopaedic Association is the voice of trauma and orthopaedic care in the UK. It supports its members but more importantly is there to ensure the highest standards and availability of care for all patients who undergo operative procedures.

It is perhaps unfortunate that an invited "clinician expert" views were given more weight than perhaps appropriate when in fact their clinical experience and publication record in the field of ACI is limited. In future the BOA would be happy to work with NICE to identify appropriate "experts" to provide informed well balanced opinions on matters or technologies deemed to be within the remit of trauma and orthopaedics.

Yours Sincerely

[redacted]

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Date: 31 of March, 2015

OUR REFERENCE: Comment by the Cell Therapy Catapult on the ACD "Autologous chondrocyte implantation for repairing symptomatic articular cartilage defects of the knee (including a review of TA89) [ID686]"

OUR COMMENT:

"Cell therapies have the potential to deliver long-term benefits to the patient and the healthcare system; however long-term value claims can be compromised when the available clinical evidence is of a shorter term (as in the case of ACI). The NICE DSU support document 14, (March 2013) describes a number of methods for performing extrapolations with patient-level data and emphasizes the importance of assessing the plausibility of extrapolated data through clinical expert opinion and biological plausibility in conjunction with sensitivity analysis. We believe there is a need for clarification about how clinical opinion and biological plausibility are factored alongside the survival analysis modelling methods described so that manufacturers are better guided in substantiating long-term claims.

Furthermore genuine risk-sharing mechanisms (rather than mere discounts) could both encourage innovation and mitigate risk for both the healthcare system and the manufacturers. We suggest a risk-sharing/patient access scheme is considered in the case of ACI".

Comments from Healthcare Improvement Scotland on: Appraisal Consultation Document

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

Comments provided by [redacted], Consultant Orthopaedic Surgeon, [redacted]

07 April 2015

1. Section 4.5 on TIG/ACT trial. The results show no significant differences overall and there were more adverse events in the ChondroCelect group. There were better results for ChondroCelect patients with a symptom history shorter than 3 years, but the natural history of chondral lesions is not well documented so these patients might have experienced symptomatic improvement even without treatment.
2. Section 4.7. Same comments apply to an uncontrolled report of use of ChondroCelect in patients with chondral defects. No control group, limited documentation of natural history of these lesions makes results difficult to interpret.
3. However it is worth pointing out that in the assessment report considered in the meeting of February 10th the assessment document contains the information "Three case series (refs 34-36) reported high levels of return to activities after cartilage injuries after 14 year, 9 years and 9 years respectively" and this refers to patients who had no cartilage surgical procedure. In one of these studies Maletius reported a case series of young athletes (mean age 25, range 14-38) who had no treatment. Fourteen years later, most (21 out of 28) had returned to activity and 22 had excellent or good function. The assumption that patients with chondral lesions have a poor prognosis is not borne out by this literature although I would concede the data is limited.
4. Section 4.10. The MACI product is not currently available on the European market as the parent company have closed the Danish laboratory that was providing the product.
5. In section 4.15 there is a commentary on the ACTIVE trial. This trial showed no difference in the first 4 years between the ACI and microfracture groups. There was a difference in favour of ACI at 5 years. However I would point out that the number of patients with this duration of follow-up would be relatively small. We were told during the February 10th meeting that the reason for the long duration of time before

benefit was observed was that the cartilage matrix took this long to regenerate. This however would not be consistent with other trials and case series that report favourable symptomatic responses at 6 – 12 months. I do not understand how it can plausibly be argued that one trial would indicate it takes over 4 years for ACI to regenerate the cartilaginous matrix and other trials show benefit within 2 years. Both cannot be correct?

6. There are other inconsistencies in the literature. Bentley et al in 2012 reported the 10 year results of ACI vs mosaicplasty with a failure rate of 17% at 10 years in the ACI group. This was a trial involving in 100 patients. However in 2014, from the same unit as the trial with some of the same authors the failure rate of a much larger case series of 827 patients with a failure rate at 10 years of 50%. Same unit, same surgery, same surgeons – and a radically different outcome in a much larger series of patients. How do we interpret this?
7. In section 4.21 we are told the economic model estimates the cost of cell harvest at £722.45 and the cost of the implantation procedure at £109.65. I am not sure how these figures are derived but the cost estimate of cell implantation seems likely to be wrong. The cell harvest procedure is a minor quick arthroscopic procedure whereas the reimplantation is a longer procedure most often performed as an open procedure. I fail to understand how this more complex procedure is estimated to cost little more than a seventh of the more minor harvesting operation. I would also disagree that failure after microfracture would be followed by a further microfracture procedure. I would say that most surgeons would be inclined not to attempt a repeat of a procedure which has already failed and would opt to either continue nonoperative treatment or perhaps offer an osteotomy.
8. I would therefore disagree with the statement in 4.22 that "the economic model in the ChondroCelect submission was logical, and was backed by mostly plausible assumptions". The statement "it was reasonable to assume that microfracture is the only relevant comparator for ACI" ignores the fact that many surgeons might choose to offer patients mosaicplasty as an alternative.
9. In section 4.25 we are asked to believe ACI is more cost effective than microfracture with no difference in the first 4 years of the ACTIVE trial between the 2 treatments and based on less than 30 patients in each treatment arm with longer term follow-up. This is not a conclusion based on robust data.
10. In section 5.5 there is a reasonable summary of the discussion regarding short and longer term outcomes after ACI. However the explanation that that ACI takes longer to become effective because the cartilaginous matrix takes longer to develop is not consistent with some studies showing early benefit. What is the explanation for this? A sceptical explanation might be that the procedure is of little value and early benefit can be attributed to a placebo effect and the late improvement is due to the variation in symptoms associated with the natural history of chondral lesions where symptoms commonly wax and wane over time.
11. Section 5.14 "literature-based estimates of the rates of knee replacement surgery vary widely in people with cartilage damage". True but the fact remains that the

requirement of TKR in the UK population overall is 0.1% so the risk of requiring TKR is low.

12. Section 5.23. This conclusion is a good summary of the status of ACI at the present time. It should only be used in the NHS in well-designed clinical trials that are likely to confirm or refute its efficacy in the treatment of symptomatic chondral defects in the knee. In the following section on key conclusions I have no amendments to suggest.

Some comments on the ACD for ACI

These relate to the Consideration of evidence section 5.

Para 5.2 says

"The Committee heard from clinical experts that there are no UK or internationally accepted treatment guidelines on how and when to treat cartilage lesions....".

I don't think that is quite correct. The BASK consensus document has received widespread support. A copy was provided to NICE and the key conclusions were reproduced, as academic in confidence, in the assessment report. The document will be published shortly in The Knee.

Para 5.2 also says "that it was difficult to specify the most appropriate treatment choice based on lesion size alone". However, mosaicplasty is limited to small defects because of damage to donor sites.

Para 5.3 refers to "3 small studies" but SUMMIT with 144 and TIG/ACT with 118 patients don't seem that small for surgical trials.

Para 5.4 says "..clinical experts stated that there was some evidence to show that ACI is clinically effective, but also stated that this evidence was not definitive"

and

"The Committee concluded that there was uncertainty in the short-term clinical effectiveness of ACI..."

I think that is wrong, that ACI has been shown to be effective, and that the issue is around effectiveness and costs relative to microfracture.

Para 5.7 says that "the claimed advantages of ACI over MF for larger lesions was not supported by the data from a study by Minas 2009". Actually, the Minas paper says in Conclusions, that,

"Larger lesions, however, seem less effectively treated with marrow stimulation."

The SUMMIT trial reported that ACI was better than MF in larger lesions (assessment report page 48). The most recent systematic review of ACI versus MF (Oussedik 2015) reports that in lesions greater than 4cm^2, ACI is more effective than MF.

Para 5.8 has an odd statement that "the Assessment Group definition of response was likely to disadvantage MF because of the lower rate of KOOS response compared with ACI". KOOS is an accepted method of assessing outcomes, so if KOOS response is poorer after MF, that is meaningful.

Para 5.8 also states;

“However, the Committee concluded that neither definition of response used in the 2 models was ideal and that this critical variable resulted in different pathways and assumptions and, ultimately, led to significant uncertainty in the cost-effectiveness results”.

We don’t think there was significant uncertainty in the CE results. We and SOBI used two different definitions of response and we had slightly different pathways and assumptions, but we think both models are robust, apart from the inappropriately early use of TKR in the SOBI model. SOBI revised their model after our comments. Both models conclude that ACI is cost-effective (within NICE thresholds).

Para 5.9 says that the treatment pathway in our model does not reflect clinical practice, but the ACD does not say what "a more accurate treatment pathway" is.

It may relate to second repairs. Para 5.11 says

"there was limited evidence on the efficacy of a second repair"

which I think is incorrect. Most of the early trials of ACI (for example Bentley et al) were in people who had had prior unsuccessful repairs, often several, but who got benefit from ACI.

Para 5.11 also disagrees with our conclusion in the assessment report, that people who have had previous microfracture have poorer outcomes after ACI, whereas I think there is reasonably good evidence on that, for example in the Minas 2009 paper. The Committee then concludes that "there was considerable uncertainty about the clinical effectiveness of the second procedure."

Para 5.17 rejects our assumption that the benefits of MF decline after 5 years, and says that assumption favours ACI. We assumed that most patients would get initial benefit from MF but that after 5 years the repair would deteriorate. We assumed that the benefit from successful ACI would last much longer, and the Bhosale paper from Oswestry supports that - improvements in Lysholm scores after ACI were maintained for up to 9 years (the longest follow-up they had). Conversely, a systematic review by Goyal (2013) reported that MF gave good short-term results in small lesions but that after 5 years, treatment failure was expected with MF irrespective of lesion size.

We disagree with the statement that;

“The Committee concluded that reducing the utility value for MF after 5 years was arbitrary and inappropriately favoured ACI.”

We could argue about which utility value to use, but given the evidence for the decline of benefit of MF after 5 years, the decision was not arbitrary. Indeed, it was evidence-based. In addition to the systematic review by Goyal mentioned above, a recently published case series with median 12 year follow-up after MF (Solheim 2015) reported that almost half had poor long-term results (either poor Lysholm scores or had to have TKR). Solheim and

colleagues advised “caution in recommending MF for articular cartilage defects, especially in subgroups with poor prognosis”.

In the sensitivity analysis wherein we extended the duration of benefit in initially successful MF by using a utility value of 0.817 for year 5 and beyond, the ICER increased to over £20,000, still within the range usually considered acceptable by NICE.

5.18 – “the Committee concluded that there was considerable uncertainty about the validity of the modelled absolute utility values used to reflect the type of person who would have ACI in England” – but the models reflect the average age of patients who have an ACI. When we varied the age, the ICER didn’t change. The Committee was told that many patients in trials were athletes, but that reflects the fact that a large proportion of people with chondral defects incurred them in sports injuries.

[redacted], March 18th 2015.

Solheim E, Hegna J, Inderhaug E, Oyen J, Harlem T, Strand T. Results at 10-14 years after microfracture treatment of articular cartilage defects in the knee. *Knee surgery, sports traumatology, arthroscopy : official journal of the ESSKA*. 2014.

Oussedik S, Tsitskaris K, Parker D. Treatment of Articular Cartilage Lesions of the Knee by Microfracture or Autologous Chondrocyte Implantation: A Systematic Review. *Arthroscopy*. 2015.

Goyal D, Keyhani S, Lee EH, Hui JH. Evidence-based status of microfracture technique: a systematic review of level I and II studies. *Arthroscopy*. 2013;**29**(9):1579-88.

Response from Leela C Biant. BASK Representative Clinician Expert.

Comments on the ACD on Autologous chondrocyte implantation for repairing symptomatic articular cartilage defects of the knee.

The consultation document above

1. Has not taken into account all the relevant evidence
2. Has not appropriately interpreted the evidence
3. The provisional guidance is entirely unsound
4. The suggestions for further research are inappropriate and unethical

Errors in the ACD

2.7 and 5.3 "There are no UK guidelines or internationally accepted treatment on how to treat cartilage lesions"
The Committee was provided with the UK Cartilage Consensus Paper, which is in press. It is due to be published in April 2015. It had 72 signatories of clinicians involved in cartilage repair in the UK at the time it was submitted to NICE. It now has close to 100, which represents the majority of orthopaedic surgeons who perform this surgery. The Dutch Orthopaedic Society and the German Orthopaedic Society have previously published similar papers.
One of the reasons the UK Cartilage Consensus Meeting was convened, was due to the previous NICE Appraisal being cited by NHS and other health providers to deny patients access to treatments where the clinicians consider the evidence to be strong enough to recommend ACI in appropriate patients. There is considerable variation in access to these services across the UK. Furthermore, clinicians were concerned that doing comparator treatments such as microfracture is less effective and compromises the chance of subsequent repair with ACI.

4.1 The Committee's summary of the AG review of clinical evidence demontrates misinterpretation of the AGs evidence.
First generation ACI (ACI-P) has a higher rate of patch hypertrophy which is amenable to correction by day-case arthroscopy, but there is no higher failure rate of the repair itself. There are comparative trials of different forms of ACI which show no difference in clinical result.
The AG stated CONCLUSIVELY from their review that ACI was more effective than microfracture. The opposite is stated in 4.1.

4.6 The summary suggests that the AG regard the TIG/ACT trial as good quality. This is true. "However, the AG regards ACI-P as obselete". This implies that the trial is now irrelevant to the current therapy. This is a misinterpretation of the AG evidence and the clinical situation.
ACI-P uses a different patch than ACI-C or MACI. The repair is just as good with ACI-P, as stated in the AG addendum, but the small complication of patch hypertrophy is much less in ACI-C and MACI, which is one reason they are favoured now. The trial is of relevance and should not be discounted or considered less valuable on these grounds. In fact, any evidence from this study is that shows the superiority of ACI over microfracture is likely to be greater

with ACI-C or MACI, as stated in the AG report. There is no difference in the re-operation rate between ACI-c and ACI-P in the ACTIVE Trial.

Publication	Comparison	Results
Schneider et al. Orthop. Ihre Grenzgeb. 2003	ACI Gen I vs ACI Gen III	No difference
Bartlett et al. JBJS(Br) 2005	ACI Gen II vs ACI Gen III	No difference
Gooding et al. Knee 2006	ACI Gen I vs ACI Gen II	No difference
Zeifang et al. AJSM 2010	ACI Gen I vs ACI Gen II	No difference

5.2 "The Committee did not consider best supportive care (including physiotherapy) to be a relevant comparator because the Committee heard that best supportive care had already failed by the time clinicians consider ACI"
6.3 " Further research is recommended to compare ACI, mosaicplasty and microfracture with conservative treatment"

The ACD contradicts itself entirely here. It was explained that surgeons do not consider surgery unless conservative methods have failed. It is therefore illogical, if not unethical to recommend research against a comparator treatment the patient has already failed by the time the present to the clinician and the Committee itself does not consider an appropriate comparator.

5.3 "It (The Committee) noted 3 small studies with relatively short follow-up"
These studies are not small surgical studies, and should not be benchmarked against drug studies. The studies mentioned are adequately powered, appropriate and methodologically sound enough to show a difference between ACI and microfracture. Indeed they all have, even at 'relatively short follow-up". If longer follow-up evidence is required, there are cohort studies and an RCT against mosaicplasty with data at minimum 10 years, and a total of 15 RCTs involving ACI.

Publication	Comparison	Results	Period
Visna et al. Acta Orthop. Belgica 2004	ACI Gen III vs Abrasion	ACI better	1 year
Knutsen et al. JBJS(Am) 2007	ACI Gen I vs MFX (in arthritis)	No difference	5 years
Basad et al. KSSTA 2010	ACI Gen III vs MFX	ACI better	2 years
VanLauwe et al. AJSM 2011	ACI Gen I vs MSF	ACI better	5 years
Cole et al. AJSM 2011	ACI Gen IV vs MFX	ACI better	2 years
Crawford et al. JBJS(Am) 2012	ACI Gen III vs MFX	ACI better	2 years
Saris et al. AJSM 2014	ACI Gen III vs MFX	ACI better	2 years
Lim et al. Clin Orthop Rel Res 2012	ACI Gen I vs MFX vs Mosaicplasty	No difference	1 year
Horas et al. JBJS(Am) 2003	ACI Gen I vs Mosaicplasty	No difference	1 year
Bentley et al. JBJS(Br) 2003	ACI Gen I vs Mosaicplasty	ACI better	2 years
Dozin et al. Clin J Sports Med. 2005	ACI Gen I vs Mosaicplasty	No difference	1 year
Bentley et al. JBJS(Br) 2012	ACI Gen I vs Mosaicplasty	ACI better	10 years

4. 5.3 “Lysholm, Tegner and Cincinnati scores were not regularly used in clinical practice and some were of limited relevance to the general population with cartilage defects” This is a misinterpretation of what the clinician experts reported. These measures were used in cartilage repair patients in earlier studies before articular cartilage-specific scores were developed. The Lysholm Score has been validated in patients with chondral leasions (Kocher MS et al JBJS Am 2004). They were used for general soft-tissue knee problems including meniscal damage or ligament damage and reflect pain and function in an active population (as opposed to an elderly arthritic population). They are reasonable measures of pain and function and allow intra-study comparison between treatments and comparison between studies.

   5.3 “The Committee concluded that, although there is more clinical-effectiveness data than at the time of the previous NICE technology appraisal guidance on the use of ACI for the treatment of cartilage defects in the knee joints, the evidence base for the technology is still emerging”
   The Committee seem to have only considered 3 RCTs against microfracture and have ignored the large evidence base on ACI clinical effectiveness (several long-term cohort studies over 10 years and an RCT against mosaicplasty at minimum 10 years. There are 15 published RCTs of some form of ACI against a comparator). The RCTs favour ACI, and the several cohorts over 10 years would suggest that the evidence has already emerged. This conclusion is also in direct contradiction to the AG conclusion of the evidence base.

   5.4 “The Committee heard that the clinical experts differed with respect to how effective they perceived ACI to be compared with microfracture. The Committee heard that this may in part reflect a clinician’s experience and preference. When asked to judge the clinical effectiveness of ACI, clinical experts stated that there was some evidence to show that ACI is clinically effective, but also stated that this evidence was not definitive. They also stated that, although ACI, microfracture, and mosaicplasty were probably clinically effective, evidence was lacking for the natural history of lesions treated by debridement and lavage”

   This is absolutely not what the clinicians expressed. It was the stated opinion of one of the clinicians present, not the other two who were given insufficient opportunity to respond, because one had to leave part-way through the meeting (having been invited at too short notice to cancel a clinic) and because the other was part of the AG, who are not invited to make any presentation. The one clinician is not representative of the vast majority of surgeons who perform this surgery, and who have put their signatures to the UK Cartilage Consensus Paper. The Committee may have given too much weight to the opinion of one, who was in contradiction with the majority of surgeons, the evidence in the literature and the AG.
   The evidence for ACI is solid and multiple, and irrespective of preference and experience and is absolutely definitive. Around 100 clinicians have signed the UK Cartilage Consensus Paper.

“They also stated that there was evidence lacking for the natural history of lesions treated by debridement and lavage”
This is not an accurate interpretation of what was said, nor is it accurate based on the literature. Large cartilage lesions become arthritis

5.5 “The Committee noted that it was presented with no clinical effectiveness data beyond 5 years” and “insufficient long-term evidence to support a conclusion on the long-term effectiveness of ACI”
This data is available, and the Committee should avail itself of this. The AG or two of the clinical experts could have presented this had they been asked.

5.7 “It (The Committee) noted that the claimed advantages of ACI over microfracture in its use for larger lesions was not supported by the study of Minas and colleagues (2009)”
The paper by Minas has been misinterpreted entirely by the Committee, and the paper in fact has evidence exactly to the contrary.

5.8 and 5.10 “significant uncertainty in the cost-effectiveness results” (of the AG)
I know as a co-author of the assessment report that the economic modelling of the AG has itself been independently assessed for quality and has been deemed to be of very good academic quality with a score of 5/6 by an independent referee chosen by the HTA programme editors.

6.3. “Further research is recommended to compare ACI, mosaiclasty and microfracture with conservative treatment, for example, sham (placebo) procedure, lavage and debridement, or intensive physiotherapy that reflects the rehabilitation following ACI”
This is illogical, and likely unethical. The Committee itself has already stated that conservative measures are an inappropriate comparator in section 5.2 “The Committee did not consider best supportive care (including physiotherapy) to be a relevant comparator because the Committee heard that best supportive care had already been failed by the time clinicians consider ACI”

NICE has not taken into account all the available evidence and has not accurately interpreted the evidence presented to it. The guidance is inappropriate and will deny effective treatment to patients, based on their flawed interpretation of clinical effectiveness data. The Committee was, perhaps, also inappropriately influenced by a clinician who did not represent the majority view, nor a sound evidence base for his statements.

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

Comments

1. Section 4.5 on TIG/ACT trial. The results show no significant differences overall and there were more adverse events in the ChondroCelect group. There were better results for ChondroCelect patients with a symptom history shorter than 3 years, but the natural history of chondral lesions is not well documented so these patients might have experienced symptomatic improvement even without treatment.
2. Section 4.7. Same comments apply to an uncontrolled report of use of ChondroCelect in patients with chondral defects. No control group, limited documentation of natural history of these lesions makes results difficult to interpret.
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6. There are other inconsistencies in the literature. Bentley et al in 2012 reported the 10 year results of ACI vs mosaicplasty with a failure rate of 17% at 10 years in the ACI

group. This was a trial involving in 100 patients. However in 2014, from the same unit as the trial with some of the same authors the failure rate of a much larger case series of 827 patients with a failure rate at 10 years of 50%. Same unit, same surgery, same surgeons – and a radically different outcome in a much larger series of patients. How do we interpret this?

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12. Section 5.23. This conclusion is a good summary of the status of ACI at the present time. It should only be used in the NHS in well-designed clinical trials that are likely to confirm or refute its efficacy in the treatment of symptomatic chondral defects in the knee. In the following section on key conclusions I have no amendments to suggest.

Comments received through the NICE website

Name	[redacted]
Role	[redacted]
Job title	Prof of reconstructive medicine
Location	Europe
Conflict	No
Disclosure	Disclosure: [redacted] is one of the senior authors of various cartilage papers including both the Tigenix as well as the Sanofi ACI trials. He served on many governance positions including that of President of the ICRS. His department has received trial support for cartilage studies and for the registration trials. He has received consultancy and teaching fees related to the topics and companies involved in this procedure 2008 - 2011. He does not have any personal shares/options royalties or such nor do any personal relations or family members. He has no current conflicts of interest at the time of this reply/comment.
Comments	Dear NICE committee members It is with respect for the amount of detail and impressed by the width of the topic covered that I have studied your preliminary document and the committee papers. As one of the leading authors of publications evaluated in your work and past president of the International Cartilage Repair Society (ICRS) I feel we have a combined responsibility to ensure proper conclusions are made and final position is described. It is of paramount importance that not only the UK healthcare, clinical, strategical or financial drivers in this judgement are considered but that one also appreciates how NICE guidance is viewed by other regulatory bodies and insurance carriers in the EU and elsewhere. Hoping to further improve the final document and help reach a correct status and create a pathway forward I have chosen to provide some suggestions and comments. These merit consideration and would help make refinements in some essential aspects of the text and choice to be made. Ad 1.1 Since ACI using the MACI and ChondroCelect products are both registered as ATMP under EMA regulations and EU law and have thus passed all requirements for standard clinical implementation we should refrain from using wording such as experimental and in research only. ACI has a long standing well established history and from the first generation techniques longterm follow up has been published which shows longterm efficacy of over 13 years average and more than 20 years outcomes. The preliminary wording in 1.1 should be changed to allow implementation in standard care using broadly accepted treatment algorithm applicable to the local situation and selected centers for cases with high complexity and additional needs. Proposed wording: — Autologous chondrocyte implantation is recommended for repairing symptomatic articular cartilage defects of the knee. Compulsory nationwide registration of use, adverse effects and efficacy is mandatory and regular reporting to the EMA advised. Observational studies and registry input should be designed to confirm the long-term clinical and economic benefits of autologous chondrocyte implantation. ACI should be used according to the UK national guidelines as developed and published by the committee of professionals and subscribed to by over 100 active experts in the field

	Ad 2.4 There is a typing error or serious mistake in the microfracture indication in section 2.4. This now reads Microfracture is normally used for lesion sizes of less than 13 cm2. This is incorrect and should read Proposed wording: 1-3 cm2. Since Mfx is absolutely not prefered for larger defects. Mosaicplasty (also known as osteochondral transplantation) involves transplanting small sections of cartilage and underlying bone from a less weight-bearing part of the knee into the damaged area. Mosaicplasty is used for small areas of damage (less than 4 cm2). This is not common practice since 4 cm is considered a large defect size and donor site morbidity in the less weight bearing area would be unacceptable. Thus if used at all Mosaicplasty is currently applied to osteochondral defects in which 1-2 plugs can completely fill the symptomatic defect. Proposed wording : Mosaicplasty can be used for small areas of damage (less than 2 cm2) and is indicated mainly for osteochondral lesions. Ad 2.5 Biopsies are not only take from the less weight bearing region if such exists. Literature and common practice have established biopsy from the defect rim as effective as well as using the vital cartilage from the loose body present in some ACI indications. EMA regulation for the EU dictates that any ATMP and thus all ACI products are required to include a GMP/GCP compliant process including viability/potency/efficacy markers. Thus patients, providers, policymakers and payers are assured that the transplanted cells have and over 95% viability and cartilage repair potency. Proposed wording: ACI involves taking a biopsy of cartilage from the affected knee during arthroscopic surgery. Chondrocytes from the cartilage are then cultured in a laboratory to increase their number. Cultured expansion should abide by GMP/GCP compliant EMA regulation and include viability, potency initial efficacy biomarkers. Finally, the chondrocytes are implanted into the area of damaged cartilage during a second surgical procedure using a biological or biomaterial cover with proper fixation to allow for cell attachment.. ACI is not indicated for degenerative arthritic joints. Ad 2.7: There is a well performed UK consensus treatment guideline which has active support of over 100 expert professionals in the clinical field. In addition national treatment guidelines, therapy advice or consensus statements have been published and are in use for Belgium, The Netherlands, Germany, Spain and the United States of America. Proposed wording: There are well described UK guidelines and internationally accepted treatment algorithms on how and when to treat cartilage lesions. Cartilage repair treatment should be selected for individual patients according current the most up to date UK published consensus. Ad 4.1 The conclusion described in this section is unfair, simplistic and does not do justice to the rigorous investigation and increasing quality of studies published in this innovative field for which methodology is still being developed. Traditional RCT guidelines and Pharma based methodology cannot be simply be applied to surgical investigations of ATMP and cell therapy. Comparator selection is debatable, samples size calculations are correct and thus study size cannot be deemed small if the predefined statistical analysis plan was correct and followed. Then conclusions are valid. Also one must remember in the initial statement 200-500 patients annually in the UK are expected thus trials including 120-150 patients are considered to be adequate and for randomized surgical trials even

	large. Lack of allocation concealment is impossible in surgical comparison of such various techniques, and does not fit within needs for informed consent. Patient reported outcomes are used for clinical efficacy thus blinding of assessment scoring is not realistic. The two largest regulatory submission approved trials for ChondroCelent and for MACI have been peer reviewed and published in the highest impact factor journals in this field, awarded best international research in the field by the largest scientific society, accepted as proof of structural superiority as well as clinical superiority by EMA and thus provide acceptable evidence to conclude that ACI comparable or better than microfracture and mosaicplasty and can be the preferred method of treatment in selected patients. Proposed wording: Therefore the Assessment Group considered the effectiveness of ACI to be comparable or better when compared with microfracture for larger size defects. Ad 4.2 Agree with summary and propose only one point which needs change to reflect literature and professional interpretation ï‚· People with small lesions had better outcomes with microfracture than people with bigger lesions. ï‚· Among people with larger lesions, ACI appeared to produce better outcomes compared with microfracture. Ad 4.6 The primary outcome of the TigACT trial was structural superiority on histological analysis and clinical non inferiority at 1 year on overall KOOS. This was met and the trial showed significantly better tissue structure from ACI than after Mfx. With subsequent predefined clinical PROMs evaluation at 5 years we were able to show durability of the repair and the significant better outcome in patients treated earlier. This being the first trial and first registered ATMP in a then still undeveloped field must be remembered when we now judge studies designed in 2000 and from which we have learned much and improved both subsequent trials and clinical treatments. The use of words such as obsolete is inappropriate and taint the paragraph as if the treatment and trial results were obsolete which is not the case. Also the use of periosteal cover although not preferred is still a viable option and n the USA even imperative since the synthetic collagen covers are not registered there yet. Proposed wording: The use of ChondroCelect after the TIG/ACT study was registered including a synthetic cover because periosteum has no obvious clinical advantages over second or third generation ACI, needs more time in surgery, and is associated with higher subsequent costs (for example, shaving of hypertrophy). Ad 4.1 The conclusion described in this section is unfair, simplistic and does not do justice to the rigorous investigation and increasing quality of studies published in this innovative field for which methodology is still being developed. Traditional RCT guidelines and Pharma based methodology cannot be simply be applied to surgical investigations of ATMP and cell therapy. Comparator selection is debatable, samples size calculations are correct and thus study size cannot be deemed small if the predefined statistical analysis plan was correct and followed. Then conclusions are valid. Also one must remember in the initial statement 200-500 patients annually in the UK are expected thus trials including 120-150 patients are considered to be adequate and for randomized surgical trials even large. Lack of allocation concealment is impossible in surgical comparison of such various techniques, and does not fit within needs for informed consent. Patient reported outcomes are used for clinical efficacy thus blinding of

	assessment scoring is not realistic. The two largest regulatory submission approved trials for ChondroCelent and for MACI have been peer reviewed and published in the highest impact factor journals in this field, awarded best international research in the field by the largest scientific society, accepted as proof of structural superiority as well as clinical superiority by EMA and thus provide acceptable evidence to conclude that ACI comparable or better than microfracture and mosaicplasty and can be the preferred method of treatment in selected patients. Proposed wording: Therefore the Assessment Group considered the effectiveness of ACI to be comparable or better when compared with microfracture for larger size defects. Ad 4.2 Agree with summary and propose only one point which needs change to reflect literature and professional interpretation ï‚· People with small lesions had better outcomes with microfracture than people with bigger lesions. ï‚· Among people with larger lesions, ACI appeared to produce better outcomes compared with microfracture. Ad 4.6 The primary outcome of the TigACT trial was structural superiority on histological analysis and clinical non inferiority at 1 year on overall KOOS. This was met and the trial showed significantly better tissue structure from ACI than after Mfx. With subsequent predefined clinical PROMs evaluation at 5 years we were able to show durability of the repair and the significant better outcome in patients treated earlier. This being the first trial and first registered ATMP in a then still undeveloped field must be remembered when we now judge studies designed in 2000 and from which we have learned much and improved both subsequent trials and clinical treatments. The use of words such as obsolete is inappropriate and taint the paragraph as if the treatment and trial results were obsolete which is not the case. Also the use of periosteal cover although not preferred is still a viable option and n the USA even imperative since the synthetic collagen covers are not registered there yet. Proposed wording: The use of ChondroCelect after the TIG/ACT study was registered including a synthetic cover because periosteum has no obvious clinical advantages over second or third generation ACI, needs more time in surgery, and is associated with higher subsequent costs (for example, shaving of hypertrophy). Ad 5.3 Final sentence is derogatory to current evidence and decennia of clinical outcomes and satisfied patients. As time, technology and treatment application progress clearly evidence and supportive data will be emerging. That by no means should infer that current proof is insufficient for implementation of ACI in NHS care. One could even argue that it would be unethical not to provide that EMA approved EU registered clinically successful and when implemented correctly cost effective therapy to a wider patient population. Why would patients be further studied or have been randomized if only the resulting convincing science were to be blocked by scientifically framed economical objections. Ad 5.4 The there mentioned experts should be presented differently since only one person was of that opinion on many aspects of the questions now generalized in the preliminary report. Thus it would be better either to query a larger group of experts on exactly these aspects or to not over exemplify the

	personal opinion of one older surgeon out of touch with this specific field. Ad 5.5 As previously mentioned and even discussed in the NICE prelim document the comm was aware and presented with long term data of very robust evidence supporting the long term efficacy of ACI. Both in the Minas data as in the Petterson data this is well described and should not be disregarded in this summary. Given all previous arguments and altered wording the final sentence of this section should be altered. Proposed wording: Since there was extensive relevant additional data on the effectiveness of ACI since the previous guidance on the use of autologous chondrocyte implantation for the treatment of cartilage defects in the knee joints, the previosuly exsisting shortcomings associated with the medium-term evidence and insufficient long-term evidence to support a conclusion on the long-term effectiveness of ACI have been addressed and thus ACI can be considered using the UK treatment algorithm within the requirement of a prospective nationwide registry. Ad 5.6 EMA guidance and EU regulation dictated that clinicians are only allowed to use ATMP registered cell therapy products. This has nothing to do with personal preference and treatment choice but is part of European law ! Thus this section needs to be altered since now it reads as if the group is unaware of these essential aspects. Ad 5.21 given the previous arguments and obvious clinical improvement from ACI as well as the many innovations in subsequent technology this section should be changed. It is beyond any reasonable doubt that ACI is proven technology and that it comprises a very visible innovation in healthcare. Two of the three currently registered ATMPs are cartilage cell therapy products. And innovation is not judged by the number of people affected but by a larger societal impact such as ACI has had on RM field since 1994 and continues to have. A recent Nature publication deemed ACI to be a clear and highly innovative example of Technovolution and thus should be considered for all intents and purposes in this document innovative, effective and established. Ad 5.23 Given all previous suggestions and the obvious need for a considerable adaptation of the final document to represent scientific and clinical reality properly we now need to re address this final paragraph. Proposed wording: The Committee therefore recommended that, because the clinical effectiveness has ben established, cost-effectiveness of ACI as applied in a well defined treatment algorithm has bee demonstrated and patient numbers for this indication are limited in the UK to 200-500 with marginal financial impact, ACI should be recommended for use in the NHS when applied following current UK consensus indications and as part of a compulsory prospective national registry. The Committee noted that these studies should generate robust outcome data and include both interventional and observational studies. Ad summary tables: due to the considerable changes proposed and the impact of such on the whole document I feel detailed comments on the final tables summary has no beneficial role at this point. These should clearly be revised once the full document refinement has been completed.

	Hoping this adds to the overall quality of the effort and of the final result, I remain respectfully available for input and questions as wells as interested in the further alterations and result of this important proceedings. [redacted] [redacted] The Netherlands

Name	[redacted]
Role	NHS Professional
Job title	Consultant Orthopaedic Surgeon
Location	England
Conflict	No
Comments	In my view the overview conclusion statement: 'Autologous chondrocyte implantation is recommended only in research for repairing symptomatic articular cartilage defects of the knee' is not justified by the evidence available and the evidence considered in the document. There has been inappropriate interpretation of the evidence and the views of knee specialists who have experience and who have knowledge of the treatment have not been adequately considered. There is now clear evidence from well powered clinical trials that ACI is better than the comparator microfracture and has a clear indication in specific situations. In addition there is clear evidence that the result of ACI when performed AFTER microfracture is worse with much lower success rate. This is mentioned in the document but not acted on. ACI should therefore be allowed as a primary treatment when indicated. There are very few patients who actually need the treatment as it is indicated in failed conservative treatment (rehabilitation) and lesions on one surface of the joint larger than 2cm square. 200 - 500 a year is a small number but a very relevant number. The data shows that quality of life and health economics can be improved by proven treatment. Specific Comments: 2.7: There are now UK guidelines produced as a consensus document by UK surgeons. This was submitted to NICE but is not referred to. I am one of the lead 4 authors on that paper. OVER 95 SPECIALIST KNEE SURGEONS HAVE AGREED WITH THE CONSENSUS DOCUMENT. "ADDITIONAL COMMENTS ON THE REPORT 3.3: cost of treatment: The cost of chondrocelect to the NHS is NOT £18,301 - it is nearer £11,000. The figure of 18K over dramaticises the cost of this effective treatment 4.2: Brilliant summary - so why not allow use of ACI? Section 4.7 onward - The Trials evidence: it is acknowledged in the document that the TIG/ACT trial showed better results that microfracture, and that the SUMMIT trial also showed better results for ACI. These are both well powered and well resourced studies done to the best scientific methodology that can be funded in the current day. Why would the document ignore these findings and

	still want more studies before recommending use of the ACI technology as primary treatment? In 4.18 the document acknowledges: The Assessment Group stated that the evidence is limited by the evolving nature of the technology, and because the longest-term data come from early versions of ACI that have largely been superseded. The Assessment Group stated that most, but not all, studies suggest that ACI is more effective than microfracture if it is used soon after the cartilage injury. How long do we have to wait for the evidence to be accepted that ACI is a better treatment?? In 4.22 and in 4.24 the document argues in favour of cost effectiveness. This is not acted on in the conclusion. In 4.36 after long analysis it is stated ACI provided greater gain in QALY. In 5.3 The Committee concluded that, although there is more clinical-effectiveness data than at the time of the previous NICE technology appraisal guidance on the use of ACI for the treatment of cartilage defects in the knee joints, the evidence base for the technology is still emerging. The Committee has commented that the RCT's were small - yet in knee surgery terms these are big, well powered and well funded. They cannot be downplayed. It was stated that the evidence base is still emerging - yes it is but the evidence NOW is very strong. The Committee has made inappropriate interpretation of the evidence summarised. In 5.4 The Committee heard that the clinical experts differed with respect to how effective they perceived ACI to be compared with microfracture. The Committee heard that this may in part reflect a clinician™s experience and preference. When asked to judge the clinical effectiveness of ACI, clinical experts stated that there was some evidence to show that ACI is clinically effective, but also stated that this evidence was not definitive. They also stated that, although ACI, microfracture, and mosaicplasty were probably clinically effective, evidence was lacking for the natural history of lesions treated by debridement and lavage It is innappropriate to base a review on published trial evidence and then take the personal view of one surgeon who says something about his own personal view - when he has never used the technology. The 95 surgeons agreeing the consensus document feel otherwise. In 5.7 It (The Committee) noted that the claimed advantages of ACI over microfracture in its use for larger lesions was not supported by the study of Minas and colleagues (2009) This is an entirely wrong conclusion of that paper - the content of which should be read. In 6.3. Further research is recommended to compare ACI, mosaiclasty and microfracture with conservative treatment, for example, sham (placebo) procedure, lavage and debridement, or intensive physiotherapy that reflects the rehabilitation following ACI There is so much evidence so far that cell treatment is effective that such a trial would be difficult to recruit to and it would be hard for a surgeon to have equipoise MORE COMMENTS IN NEXT SECTION "

	"FINAL COMMENTS TO GO WITH PREVIOUS COMMENT DOCUMENT The conclusion section seems to go against all the positive evidence presented. The Committee indicates it was not persuaded - it should need to be persuaded as the scientific data in conclusive as mentioned in the analysis. Lastly the Committee wants more observational studies in the future: yet the whole conclusion part belittles the data as it is. How can observation studies every provide the answer this Committee wants?? ACI should be funded and then trials as to how to optimise indications and how to improve outcome should be recommended The consensus document contains all these suggestions. Thank you for reading and considering this [redacted]

Name	[redacted]
Organisation	International Cartilage Repair Society (ICRS)
Role	[redacted]
Location	England
Conflict	NO
Comments	The comments herein are made on behalf of The International Cartilage Repair Society (ICRS) on request from and with approval of The ICRS Executive Committee. The ICRS is a forum for international collaboration in cartilaginous tissue research by bringing together basic scientists and clinical researchers engaged or interested in the field of cartilage biology: http://www.cartilage.org General comment We wish to state categorically that the overview conclusion statement: 'Autologous chondrocyte implantation is recommended only in research for repairing symptomatic articular cartilage defects of the knee' cannot be justified in light of the available evidence. There is very clear evidence from properly powered clinical trials that ACI is better than the comparator microfracture and that ACI has a clear indication in specific situations. It is also clear that the result of ACI when performed AFTER microfracture is worse, with much lower success rate. Whilst this is mentioned in the NICE document, it does not appear to have been taken into account. Specific comments 1. There are over 1000 papers in the literature on ACI, including three long-term cohort studies with data on patients over 10 years. These seem to have been ignored by the committee in its conclusions. 2. Warwick Evidence (commissioned by the HTA programme) concluded that ACI showed a clear benefit over microfracture and mosaicplasty and there was evidence for its use as first-line therapy in appropriate patients. This conclusion is very similar to that of the UK Cartilage Consensus Paper, which is due for publication shortly and has close to 100 signatories of clinicians undertaking care of patients with articular cartilage injury. ICRS considers that conclusion reflects view of the majority of experts in this are. Warwick Evidence was commissioned by the HTA programme on behalf of the Dept of Health to produce an economic modelling of ACI, which found it to be a cost-effective therapy.

	3. The ACD refers to 3 small studies. It is worth noting however that the Genzyme and Tigenix studies were both sufficiently powered to show a difference, and these cannot be considered as small in the context of orthopaedic surgical studies. We do not believe that the further research suggested would provide any useful evidence beyond that already published. The committee has suggested that future clinical trial design would be improved by allocation concealment. However this is not possible in this situation as one treatment (microfracture or osteochondral grafting) requires a single operation and the other (ACI) requires two operations. Blinding of the surgeon is not possible. 4. Sustained long-term beneficial results of ACI have been reported in several studies that have not been taken properly into account by the committee. These include: Minas T et al Clin Orthop Relat Res. 2014 Jan;472(1):41-51. Biant LC et al Am J Sports Med. 2014;42(9):2178-83. Peterson L et al Am J Sports Med. 2010 Jun;38(6):1117-24. Bentley G et al J Bone Joint Surg Br. 2012 Apr;94(4):504-9. Moseley JB Jr et al Am J Sports Med. 2010 38(2):238-46. Conclusions On behalf of ICRS we request that NICE re-examines the available data taking into full account all of the published studies. There also needs to be careful re-examination of the proposed additional research that is needed as it appears to have been proposed with no real understanding of the design limitations in surgical clinical trials in general and cartilage repair surgery in particular. [redacted] Approved and co-submitted by other members of the ICRS Executive Committee

Name	[redacted]
Role	Orthopaedic surgeon working with chondrocyte implantations clinically since 1987
Job title	Professor, MD, PhD
Location	Europe
Conflict	Yes
Disclosure	Consultant in cartilage repair to Sanofi Genzyme (MACI) Investigator in the Summit trial Working clinically with ACI in hyaluronic acid matrice
Comments	I have been working with cartilage repair for almost 30 years and in basic science as well as in clinical research and practice. I have been using autologous chondrocyte implantation for patients since Lars Peterson and I did the first ACI in October 1987 in Gothenburg with cells cultured by Professor Anders Lindahl. It is with great interest I have read the comprehensive consultation document. I have some comments to the text, please see below.

	1 Appraisal Committee™s preliminary recommendations 1.1 Autologous chondrocyte implantation is recommended only in research for repairing symptomatic articular cartilage defects of the knee. Research should include clinical trials and observational studies designed to measure the long-term benefits of autologous chondrocyte implantation. Comments: Autologous Chondrocyte implantation was first introduced to the world in October 1987 by our group in Gothenburg (Lars Peterson, Mats Brittberg, Anders Lindahl). Since then several thousands of patients have been operated with that method all over the world. From the first generation of ACI with cells injected as a suspension in under a periosteal membrane to second generation of ACI with cells under a collagen membrane to now 3rd generation ACI with cells seeded on or in matrices. The ACI technology has further been evaluated in the last 10 years with 15 different randomized studies. Eleven of those studies have been ACI versus another repair technique. In 7/11 of those studies, ACI showed a significant superiority over the other technique. Seven of the studies were ACI versus microfracture (MFX) and of those studies ACI was significantly better in different parameters than MFX in 5/7. There are not many other orthopaedic techniques that have been so thoroughly examined. To conclude that ACI should only be used in research would then mean that most other orthopaedic operations should only be used in research meaning that also when using MFX it should also be only as a research project. As with all different operative treatments, ACI should be used with care and ACI as well as other cartilage repair treatment should be monitored in registries (national and/or international).Today, there are two ACI technologies that have been approved by EMEA. I suggest that in the text it should be noted that the approved ACI technologies are used as per their indications while other ACI variants are used in research studies until being approved by EMEA. 2.4 .Microfracture involves drilling small holes through the bone under the damaged cartilage to allow bone marrow cells to fill the damaged area and to differentiate into chondrocytes Comments: Microfracture is not drilling but a perforation of the subchondral bone plate to reach intracortical vessels. The resulting bleeding is developed into a blood clot that functions as a scaffold to attract cells from the bone marrow. Such cells could be mesenchymal stem cells that may go into a chondrogeneic lineage producing a fibrocartilaginous tissue repair. However, it is not that they become pure chondrocytes. 2.4Microfracture is normally used for lesion sizes of less than 13 cm2. Comments: Microfracture is normally used for lesion sizes of less than 3cm2! 2.5.Finally, the chondrocytes are implanted into the area of damaged Cartilage during a second surgical procedure, in the hope that they will repair the damaged area. Comments: The wording ¨in the hope that they will repair¨is not suitable as it is a degree of subjectivity from the evaluator which means that the evaluator not fully believes that the cells are involved in the repair. It is not written similarly regarding the other techniques but a certain degree of hope is also involved in those repairs..

	2.4 .Microfracture involves drilling small holes through the bone under the damaged cartilage to allow bone marrow cells to fill the damaged area and to differentiate into chondrocytes Comments: Microfracture is not drilling but a perforation of the subchondral bone plate to reach intracortical vessels. The resulting bleeding is developed into a blood clot that functions as a scaffold to attract cells from the bone marrow. Such cells could be mesenchymal stem cells that may go into a chondrogeneic lineage producing a fibrocartilaginous tissue repair. However, it is not that they become pure chondrocytes. 2.4Microfracture is normally used for lesion sizes of less than 13 cm2. Comments: Microfracture is normally used for lesion sizes of less than 3cm2! 2.5.Finally, the chondrocytes are implanted into the area of damaged Cartilage during a second surgical procedure, in the hope that they will repair the damaged area. Comments: The wording ¨in the hope that they will repair¨is not suitable as it is a degree of subjectivity from the evaluator which means that the evaluator not fully believes that the cells are involved in the repair. It is not written similarly regarding the other techniques but a certain degree of hope is also involved in those repairs.. 5.3: . The Committee further concluded that, although there is more clinical-effectiveness data than at the time of the previous NICE technology appraisal guidance on the use of autologous chondrocyte implantation for the treatment of cartilage defects in the knee joints, the evidence base for the technology is still emerging. Comments: However, on section 4.18 The Assessment Group stated that most, but not all, studies suggest that ACI is more effective than microfracture if it is used soon after the cartilage injury.Is there then enough evidence to use microfracture instead of ACI ? The evidence base of that MFX technology and all other cartilage repair is also still emerging. Recently, research has shown that deep drilling may be a better alternative than mfx. 5:16: confidential discounts sometimes provided to the NHS by the companies, making the real cost difficult to evaluate. Comments: As the costs presented in the committee report not illustrate the actual reality costs, the calculations are of less value. Remember that ACI is mostly used as a secondary procedure after that other cartilage repair methods have failed. To make a new secondary or a third surgery that may fail is very expensive and could be a catastrophe for the patient. 5:22: .The Committee therefore recommended that, because the clinical effectiveness and cost-effectiveness of ACI remains uncertain, ACI should not be recommended for routine use in the NHS unless it is part of existing or new clinical studies... Comments: In my practice, patients are referred to me due to several failed cartilage repair operations. Such patients are difficult to treat but ACI is in such occasions a possible solution. Most of the reports in the literature are on patients getting an ACI after failed other surgeries and there are long term results up to 20 years follow up. In patient treatments, there are responders and

	non “responders and the amount of studies retrospective, prospective and randomized that have been done with ACI has shown that ACI has a clinical effectiveness with long time duration in this severe patient category. If based on the committees evaluation, ACI should only be done as part of existing or new clinical studies, all other cartilage repair methods should also be done only as part of clinical studies.Engen et al. found that Knee cartilage defect patients enrolled in randomized controlled trials are not representative of patients in orthopaedic practice. For a fair use of different repair methods in the future, all cartilage repairs could be followed in arthroscopy registers like what is already done in ACL registers in the Scandinavian countries. I believe it will be easier to get the true clinical effectiveness of different methods in such register follow ups related to all methods whatever costs they present. I hope my comments may be of help for the final conclusions of the use of ACI as well as of other repair methods.Sincerely Yours, [redacted] [redacted] Cartilage Research Unit, University of Gothenburg [redacted] [redacted] [redacted] Sweden

[redacted]	[redacted]
Organisation	Japanese Orthopaedic Society for Knee, Arthroscopy and Sports Medicine
Role	Private Sector Professional
Job title	Professor
Location	Other
Conflict	No
Disclosure	President-elect, International Cartilage Repair Society
Comments	I have been working with cartilage repair in Japan. I have read the documents and I have several comments to the review team™s conclusion as follows. 1.1 Autologous chondrocyte implantation is recommended only in research for repairing symptomatic articular cartilage defects of the knee. Research should include clinical trials and observational studies designed to measure the long-term benefits of autologous chondrocyte implantation. 5:22: .The Committee therefore recommended that, because the clinical effectiveness and cost-effectiveness of ACI remains uncertain, ACI should not be recommended for routine use in the NHS unless it is part of existing or new clinical studies... Comments: There have been over 10 comparative studies of ACI versus microfracture (MF). It is notable that most recent studies (Crawford JBJS 2012, Saris Am J Sports Med 2014) showed significantly better subjective outcomes by ACI as compared with MF. This means well designed RCTs could delineate the advantage of ACI over MF and thus it is too early to conclude that ACI should only be used in research although the significance of ACI still needs be

	proved by future studies. 2.4 .Microfracture involves drilling small holes through the bone under the damaged cartilage to allow bone marrow cells to fill the damaged area and to differentiate into chondrocytes Comments: It should be noted that MF procedure could develop postoperative subchondral bone pathology such as intralesional osteophyte (Minas, Am J Sports Med 2009, Cole, Am J Sports Med 2011) and thus might not be regarded as benign procedure as has been recognized. As could be the case with autologous osteochondral plug implantation such as mosaic plasty and OATs, these procedures require the sacrifice of healthy cartilage (donor site) with equivalent size to the lesion and there have been several reports regarding the donor-site morbidity associated with the procedures (Sagstetter, J Bone Joint Surg Am 2009, Kock, Acta Orthop 2010). Likewise, this procedure might not be a benign intervention and we should not easily draw a conclusion regarding this procedure, either. In this regard, ACI procedure which does not damage subchondral bone could have theoretical advantage and thus, once again, we may need precisely to followup the patients after all the intervention available now including ACI and other options and it is too early to conclude that ACI should only be used in research. 2.5.Finally, the chondrocytes are implanted into the area of damaged Cartilage during a second surgical procedure, in the hope that they will repair the damaged area. Comments: The wording ¨in the hope that they will repair¨is not suitable as it is a degree of subjectivity from the evaluator which means that the evaluator not fully believes that the cells are involved in the repair. It is not written similarly regarding the other techniques but a certain degree of hope is also involved in those repairs.. I hope my comments may be of help for the final conclusions of the use of ACI as well as of other repair methods. Sincerely Yours, [redacted] [redacted] [redacted] Institute for Medical Science in Sport Osaka Health Science University

Name	[redacted]
Role	NHS Professional
Job title	Consultant
Location	England
Conflict	No

Comments	Options for biological repair have been available for 20 years. Yet despite this, and multiple sources citing better response with biological reconstruction, NICE deems it necessary to still classify this as "Experimental". The majority of patients who have treatable lesions have no access to such treatment on the NHS. It would appear that the current recommendations would like symptomatic patients to remain symptomatic until eventual irreversible, mutilating arthroplasty, unless they are fortunate enough to be in proximity to a research establishment. Estimating that the annual treatable portion of the population to be 200 or so is clearly a gross underestimate based on data from a period when MRIs are not as frequent as today. Costs of such treatment do not take into consideration that economies of scale mean the costs would decline as the therapy becomes mainstream. This guidance needs to be updated annually, such is the rapidity of new technologies entering the market. One example is the single stage stem cell application treatment. i.e. the Shetty Kim technique. This enhanced Microfracture using concentrated stem cells is a procedure that has an additional cost of only £1000, and has already proved effective up to 3 years from implantation. In my humble opinion, NICE should accept that this is no longer experimental study after 20 years of treatments. Guidance should be concentrating on advising on patient selection, based around long term health economic analysis. Would recommend the establishment of a Cartilage Registry in the UK, much the same way as the NJR to provide advice ad evidence that responds to the evolution of the technology in agile responsive way. I am happy to develop one if needed.

Name	[redacted]
Role	University Professor involved in basic science and research for patient benefit in biomechanics of gait
Job title	[redacted]
Location	England
Conflict	No
Comments	I am surprised and bewildered that NICE should conclude from the abundant evidence in its own report: 'Autologous chondrocyte implantation for repairing symptomatic articular cartilage defects of the knee (including a review of TA89)' that ACI is not yet sufficiently demonstrated to show long term benefits and cost effectiveness to approve its adoption as an intervention. As a scientist involved in basic research into knee biomechanics and research for patient benefit into pre- and re-habilitation for debilitating knee articular cartilage defects, and being myself a patient suffering from this condition, I am on the contrary convinced by this evidence that ACI both as a first intervention and for reintervention is a more appropriate procedure than microfracture, which is known to damage subchondral bone, and creates an biomechanically inappropriate fibrocartilage layer, which cannot by definition perform the lubrication functions of hyaline cartilage required at the knee, and which fibrocartilage layer has a short lifetime. The evidence is already there in this report that ACI is the better approach, which damages subchondral bone less and produces a biomechanically appropriate and long-lasting hyaline cartilage repair. Requiring further research which is most unlikely to get funded, particularly in the current research funding environment, will unnecessarily

	prolong implementation of a viable intervention for another decade, and thus prolog suffering of patients for no good reason.

Name	[redacted]
Role	NHS Professional
Job title	[redacted]
Location	England
Conflict	No
Comments	I do not consider that the appraisal consultation document reflects the true state of treatments for chondral defects. Whilst evidence was gathered it has not been taken into account of in a scientifically robust method. There is good evidence for the use of ACI. There are prospective randomised trials which have shown clear benefits and economic analyses have shown that this treatment is cost effective. The trials were adequately powered and with adequate follow-up. in 6.3 the report states that 'further research is recommended to compare ACI, mosaicplasty and micro fracture with conservative treatment, for example , sham (placebo) procedure, lavage and debridement, or intensive physiotherapy that reflects the rehabilitation following ACI.' This follows the committee stating in 5.2 that conservative measures are an inappropriate comparator. Mosaicplasty has fallen into disrepute as it damages other areas of the knee and fails to restore a congruent chondral surface. Microfracture is inappropriate for large lesions. ACI should be a first line treatment. This document disadvantages young patients who need chondral surfaces reconstructed to allow them to lead a normal life at home and in leisure time. UK patients have been disadvantaged following the previous NICE guidance where ACI was deemed to be experimental. Whilst stem cell therapies may be developed they are not proven either scientifically or economically.

Name	[redacted]
Role	NHS Professional
Job title	Consultant orthopaedic surgeon
Location	England
Conflict	No
Comments	You state that there are no UK or International guidelines on how to treat cartilage lesions however there are in the form of the UK Cartilage consensus paper. This supports use of ACI as a primary procedure for lesions over 2 sq cm and this is based on good long term evidence. You have commissioned your own independent Appraisal guidance and I feel you have misinterpreted the results as it quite clearly shows that not only is ACI effective it is also cost effective. This is also based on good quality evidence. ACI as shown by the Appraisal group has been shown to be cost effective using the list price of products. You have not taken into account that almost no users will pay this price, as they will receive substantial discounts, dependant on volume of use. As a result ACI will be more cost effective than you have demonstrated. I understand that you have heard evidence from one clinician who stated that there is doubt about the efficacy of ACI. I believe that this one opinion does not concur with the vast majority of surgeons who are up to date with ACI techniques

	and the literature surrounding its use. This is evidenced by the large number signing the UK Cartilage consensus paper. NICE suggest more research is required, I feel that there is enough evidence to show that it has already been demonstrated to be an effective treatment. As such it is likely that no further research will be funded and this valuable technique will simply fall into disuse. If this occurs then NICE will be responsible for denying patients a well supported proven, cost effective treatment. It is likely if treatment is denied then patients will receive a lesser treatment with poorer outcome or will be asked to contact NICE directly to ask what they should do in lieu of receiving no treatment.

Name	[redacted]
Role	NHS Professional
Job title	Senior Knee Fellow
Location	England
Conflict	No
Comments	It seems incredible to me that despite years now of thorough investigation and an excellent body of robust evidence that cartilage implantation is not recommended in day to day practice. The evidence presented to the NICE committee and recommendations by the UK consensus group must be upheld if we are to continue to look after the best interests of our patients. Cartilage implantation is not universally applicable, but where it is indicated as per the evidence, it should be recommended by NICE as first line therapy.

Name	[redacted]
Role	NHS Professional
Job title	Consultant Knee Surgeon
Location	England
Conflict	No
Comments	Dear Sirs, I do not feel all the evidence has been appropriately taken into account as all my reading and experience surrounding this treatment clearly shows better efficacy in the medium term than any other treatment for this difficult group of patients. Handcuffing this to further research which is already exhaustive will ultimately have the opposite effect and result in withdrawal of chondrocyte therapies for our generation.

Name	[redacted]
Role	NHS Professional
Job title	Consultant Orthopaedic Surgeon
Location	England
Conflict	No
Comments	As a knee surgeon, I see a large number of patients with chondral pathologies who would benefit from ACI treatment. Unfortunately there is no other alternative treatment available for young patients with large chondral defects. There is enough available evidence in literature suggesting clinical and cost effectiveness of ACI type treatments. I was hoping that after many years of wait, I would finally be allowed to offer this treatment to selected patients who have no other hope for their knee pathology. This TA review has restored status quo and would do a disservice to a large group of patients. Unfortunately, there is no other new treatment on horizon. If NICE is concerned about cost implications, use of this technology can be restricted to larger centres, with patients being referred to such centres.

Name	[redacted]
Role	NHS Professional
Job title	Consultant
Location	England
Conflict	No
Comments	Usual stupidity. The knee community jumps through hoops to prove that something works and then it is still turned down. How many more young people are going to have to suffer before we are allowed to use something that works and is cost effective? please change the guidance and allow this treatment

Name	[redacted]
Role	NHS Professional
Job title	Consultant Orthopaedic Surgeon
Location	England
Conflict	No
Comments	I believe that the evidence is fairly convincing that, for isolated contained cartilage defects in stable knees, the best quality cartilage with sustained functional improvement is achieved by ACI. This should no longer be termed "experimental" as the evidence is abundant and good quality.

Name	[redacted]
Role	NHS Professional
Job title	Consultant Orthopaedic Surgeon
Location	Scotland
Comments	Autologous Chondrocyte Implantation is an important technique that can restore articular cartilage to an injured knee. This will allow pain relief and restored function to a largely young patient group. It may delay or avoid the need for more extensive surgery such as arthroplasty. There is a strong evidence base to support it's use , but the continued collection of data, and multicentre controlled trials are very important. I strongly urge NICE to asupport the continued practice and development of ACI therapies. Not doing so would significantly disadvantage a generation of young sufferers, and would severely damage an area of clinical research in which the UK currently is one of the leaders

Name	[redacted]
Role	NHS Professional
Job title	Consultant Orthopaedic Surgeon
Location	Wales
Conflict	No
Comments	I am bemuse dat teh conclusion that this procedure has nothing to offer. We are desperately in need of biological solutions to biological problems. Bits of metal and plastic only do so much. The young and active need better solutions and in ACI we have one such. The evidence in support of it is clear. I do not understand how the conclusions have been reached.

Name	[redacted]
Organisation	Exeter Knee Reconstruction Unit
Role	NHS Professional
Job title	Consultant Orthopaedic Surgeon
Location	England
Conflict	No

Comments	It is disappointing that despite the evidence of a Consensus Paper submitted and supported by the majority of UK orthopaedic surgeons involved in treating chondral lesions, the committee still consider there to be insufficient evidence to support the use of ACI. Our EU partners disagree with the findings of your committee and have approved the use ACI technologies for treating chondral lesions for several years now, so much so that is has proved difficult to recruit patients into any further randomised studies comparing ACI with micro fracture. Sufficient evidence exists in the literature to support the superiority of ACI. (Basad et al KSSTA 2010, Van Lauwe et al AJSM 2011, Cole et al AJSM 2011, Crawford et al JBJS (Am) 2012, Saris et al AJSM 2014.)

Name	[redacted]
Organisation	NHS Professional
Job title	Consultant Surgeon
Location	England
Conflict	No
Comments	This procedure has an enormous amount of data over several decades. In selected cases (large defects in young patients with stable, well-aligned knees & menisci intact / replaced) the evidence is very strong that this is not experimental, but should be recommended as primary treatment.

Name	[redacted]
Role	NHS Professional
Job title	Knee Fellow
Location	England
Conflict	No
Comments	I disagree with the recommendations made using the available evidence that NICE has at its disposal. The evidence for ACI is compelling and only offering micro fracture instead of ACI is unethical with the evidence we have.

Name	[redacted]
Role	Private Sector Professional
Job title	Consultant Orthopaedic Surgeon
Location	England
Conflict	n/a
Comments	I have been in practice as a consultant in knee surgery for over 30 years and I have lectured in knee surgery in Australia, Brazil, Canada, Chile, China, Equador, Egypt, Greece, India, Italy, Peru, Portugal, Singapore and Zambia and operated in Egypt. I am well aware of the merits of ACI and firmly believe that in the correct hands this should now be an accepted procedure for use in the primary situation.

Name	[redacted]
Role	NHS Professional
Job title	Consultant knee surgeon
Location	England
Conflict	No

Comments	I am unclear why the appraisal does not support ACI, when independent review of the literature by the Warwick group gave support and advised ACI was an appropriate treatment , clinically effective and economically value for money.

Name	[redacted]
Role	NHS Professional
Job title	Consultant Orthopaedic Surgeon
Location	England
Conflict	n/a
Comments	Having read the assessment report prepared by Warwick evidence and the draft appraisal consultation document, I would like to share my views. There is good quality evidence that demonstrates that ACI should be recommended (shown good long term results), including for use as a first line treatment . The evidence also uses the list price for ACI products, thus the actual cost benefits will be greater than quoted as most hospitals will receive discount on their ACI products. Whilst I agree that results and patient outcomes should be audited I disagree that further "research" is required, as there is already a good level of evidence to support its use. It is unlikely that any further funding for such research will be granted, for what is considered by most to be of proven therapeutic benefit.

Name	[redacted]
Role	NHS Professional
Job title	Consultant Trauma and Orthopaedic Surgeon
Location	England
Conflict	No
Comments	This document is short sighted and ill informed. It ignores a wealth of good quality research within this field. Whilst ACI is not a panacea it is has it's place in the arthritis prevention options available to surgeons.

Name	[redacted]
Role	NHS Professional
Job title	Consultant Ortghopaedic Surgeon
Location	England
Conflict	No
Comments	As a retired knee surgeon practicing for over 30 years I found the research and clinical evidence for this procedure compelling. The number of patients in my practice with cartilage defects for whom I felt it was indicated was relatively small, so I referred patients on to surgeons with considerable experience of the technique. This is no longer a research procedure, but should be part of the standard surgical procedures for repair of cartilage defects

Name	[redacted]
Role	Private Sector Professional
Job title	Consultant knee surgeon
Location	England
Conflict	No

Comments	i had done around 60 ACI/MACI as a member of Stanmore trial between 2002-2010, both NHS and BMI HIGHFIELD private hospitals. there was 60 -70% good results. Tibio-femoral joint was better than Patello/femoral one.A lot of young people were delighted with results. ACI transformed lifes of so many people.