Cartilage defects - ACI for repairing symptomatic articular cartilage defects of the knee [ID686]

Requests for the AG prior to Appraisal Committee Meeting

At pre-meeting telephone conference, the Committee Chair and Lead Team for this appraisal decided to request the following:

1. Sensitivity analyses removing the logical inconsistencies in transition probabilities, that is, ensuring the probability of a second repair cannot exceed that of the first repair, and the probability of MF after ACI cannot be better than ACI as a first repair.

With this scenario we have changed the transition probabilities, so we have assumed that the:

1) Second repair being an ACI after a first repair of MF will be equal to a second repair ACI after a first repair of ACI i.e. transition probability changed from 0.96371 to 0.93978.
2) Second repair being an MF after a first repair of ACI will be equal to a second repair MF after a first repair of MF i.e. transition probability changed from 0.96481 to 0.85270.

As we can see from the results below (Tables 1a and 1b), the ICERs are very close to the base-case analysis which was presented.

Table 1a: Removing the logical inconsistencies in transition probabilities by scenario

Procedure	Total mean costs £	Total mean QALYs	Incremental costs £	Incremental QALYs	ICER £ (cost per QALY gained)
Deterministic - discounted					
Scenario 1					
MF (ACI)	6,607	17.0272	-	-	-
ACI (ACI)	20,921	18.0228	14,314	0.9956	14,377
Scenario 2					
MF (MF)	5,015	17.0033	-	-	-
ACI (MF)	19,892	17.9558	14,877	0.9525	15,618

Table 1b: Removing the logical inconsistencies in transition probabilities

Procedure	Total mean costs £	Total mean QALYs	Comparison	Incremental costs £	Incremental QALYs	ICER £ (cost per QALY gained)
Deterministic - discounted						
MF (MF)	5,015	17.0033	-	-	-	-
MF (ACI)	6,607	17.0272	MF (ACI) v MF (MF)	1,592	0.0239	66,613
ACI (MF)	19,892	17.9558	ACI (MF) v MF (ACI)	13,285	0.9286	14,306
ACI (ACI)	20,921	18.0228	ACI (ACI) v ACI (MF)	1,029	0.0670	15,365

2. A rationale for the use of short term data to inform long term outcomes (3 year data was used to inform year 1 TMP and 2 year data was used to inform later year TMPs). Why was 5 or 8 year data not used? Use of alternative long term data (if this is achievable) in a sensitivity analysis.

   We used the 3 year progression data from the TIG/ACT trial published in 2009 based on patients who either received ACI-P with Chondrocelect or MF to inform year 1 TMP. For the later years TMPs, we used 2 year progression data from the SUMMIT trial published in 2014 where patients either received MACI or MF. This latter publication is more relevant to the UK, as ACI-P has now been superseded by either ACI-C or MACI; however, only 2 year data is currently available; hence the need to supplement this with the publication in 2009. However, there was little difference in results between those who respond or not respond to either ACI or MF between the two studies.

   We didn't use the data from the ACTIVE trial (i.e. the 5 or 8 year data), even though they presented data on additional procedures after either an ACI or a control procedure (see Appendix Table 8). This is because we don't know at what time point this additional procedure took place, except that this time period was more than 5 years. For example, five patients had a MF after an ACI, but we don't know when after the five years the MF took place.

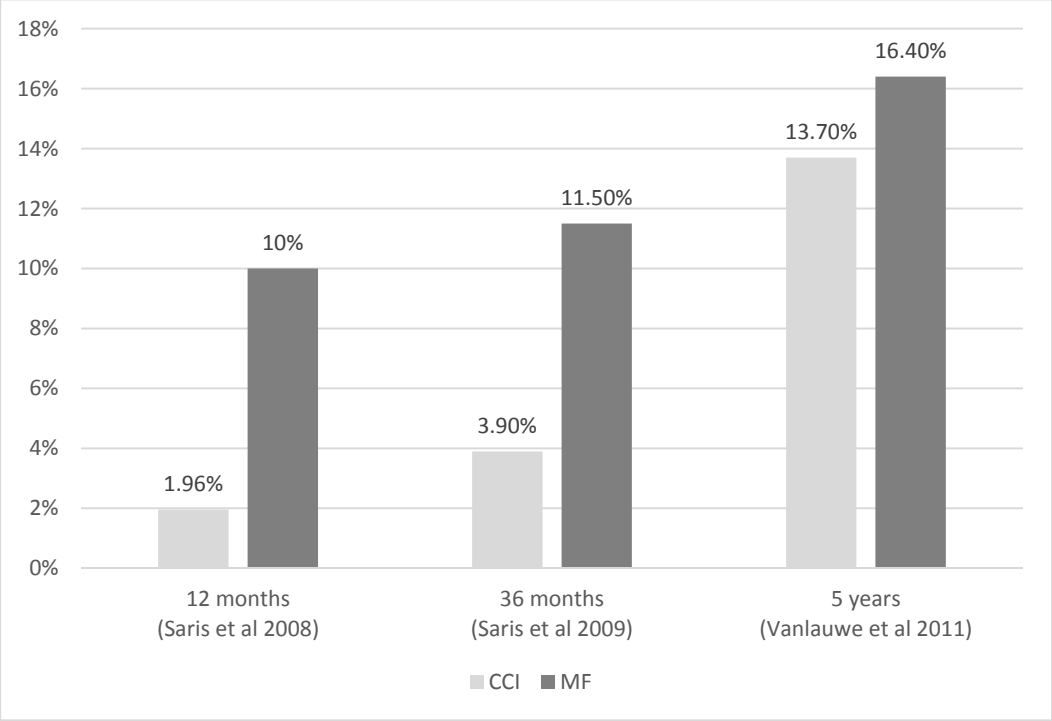
3. A graphical summary of the failure rates over time assumed in the AG model and a comparison with longer term data reported in the clinical effectiveness section (e.g. 5-year and beyond data etc).

In the clinical effectiveness section, the studies providing five years and beyond data are TIG/ACT/01/2000 study and compassionate case series. Unfortunately, the latter does not report failure rates. The data on the former was available in the three published studies namely Saris et al 2008, Saris et al 2009 and Vanlauwe et al 2011. The proportions failing the intervention at 12 months, 36 months and five years are shown in Figure 2, below. Note that failure was defined as a decision by the surgeon that another operation was necessary.

	12 months* (Saris et al 2008)	**36 months (Saris et al 2009)**	**5 years (Vanlauwe et al 2011)**
CCI	1.96%	3.90%	13.70%
MF	10%	11.50%	16.40%

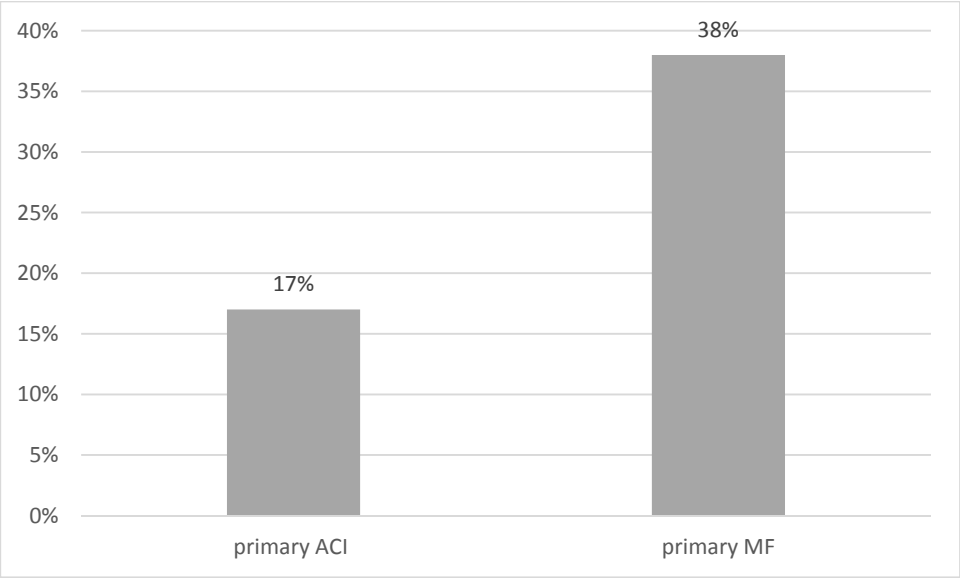
* Saris et al, 2009 also reported the 12 months data

Figure 2. Failure rate (TIG/ACT/01/2000)



The failure rate assumed in the AG model at three years is shown in Figure 3, below. Failure is defined differently from in TIG-ACT, based on the SUMMIT trial where success (called "response" in the SUMMIT report) was improvement of at least 10 points in KOOS scales. Here, only the proportion of patients failing the primary procedure has been presented. Those who fail this intervention will either undergo second repair while some will choose not to undergo another procedure. Details are in the AG report.

Figure 3. Failure rate at three years following primary procedure assumed (AG model)



4. Utility and failure rate assumptions – the AG applied a utility decrement after year 5 in the MF arm (that is, assuming the same benefit after year 5 as someone who fails at year 1). Please assess the impact of this assumption in more detail by:

We have as requested by NICE carried out a sensitivity analysis assuming that the utility after MF is maintained for much longer than in our base case. As expected, this makes MF much more competitive. However such an assumption goes against the evidence from primary studies and systematic reviews. For example;

- Harris et al 2010: "While the clinical outcomes of MF tended to either plateau or deteriorate over longer time periods, the results of ACI tended to remain stable or improve."
- Mithoefer 2009: "In athletes who returned to sports, the ability to continue at the pre-injury level after 3 to 5 years was markedly better after ACI than with MF"
- Saris 2009: "success at up to 5 years 62% MF, 78% ACI"

I. Scenario where the utility of MF in Year 5 and subsequent years = 0.817 (not 0.654)

As we can see from the results below (Tables 2a and 2b), this assumption increases the ICERs by approximately £5,000; however, ACI as a first repair is still more cost-effective than MF as a first repair (see Table 2a).

When comparing all four scenarios, if the second repair is an ACI after a first repair of MF, this is more costly and slightly less effective than if both repairs are MF; hence MF (ACI) is dominated by MF (MF) (see Table 2b). When this scenario is taken out of the equation, ACI as a first repair is still more cost-effective than MF as a first repair (see Table 2b).

Table 2a: Utility value of MF = 0.817 in year 5 and subsequent years by scenario

Procedure	Total mean costs £	Total mean QALYs	Incremental costs £	Incremental QALYs	ICER £ (cost per QALY gained)
Deterministic - discounted					
Scenario 1					
MF (ACI)	6,607	17.3089	-	-	-
ACI (ACI)	20,921	18.0228	14,314	0.7139	20,051
Scenario 2					
MF (MF)	5,015	17.3090	-	-	-
ACI (MF)	19,892	17.9833	14,877	0.6743	22,061

Table 2b: Utility value of MF = 0.817 in year 5 and subsequent years

Procedure	Total mean costs £	Total mean QALYs	Comparison	Incremental costs £	Incremental QALYs	ICER £ (cost per QALY gained)
Deterministic - discounted						
MF (MF)	5,015	17.3090	-	-	-	-
MF (ACI)	6,607	17.3089	MF (ACI) v MF (MF)	1,592	-0.0001	Dominated
ACI (MF)	19,892	17.9833	ACI (MF) v MF (ACI)	13,285	0.9286	14,306
ACI (ACI)	20,921	18.0228	ACI (ACI) v ACI (MF)	1,029	0.0670	15,365
MF (MF)	5,015	17.3090	-	-	-	-
ACI (MF)	19,892	17.9833	ACI (MF) v MF (MF)	14,877	0.6743	22,063
ACI (ACI)	20,921	18.0228	ACI (ACI) v ACI (MF)	1,029	0.0670	15,365

II. Scenarios where the utility of the "choose not to have a second repair" state is a mid-point between failure and success (and extremes where it is the same as success and the same as failure)

When altering the utility value of those that "choose not to have a second repair" and using a midpoint value of 0.7355 the results are similar to the base-case analysis; that is ACI as a first repair is more cost-effective than MF as a first repair; however, the ICERs values have increased slightly (see Tables 3a showing results by scenario analysis and 3b showing results for all four options).

Table 3a: Utility value for no second repair - midpoint value (0.7355) by scenario

Procedure	Total mean costs £	Total mean QALYs	Incremental costs £	Incremental QALYs	ICER £ (cost per QALY gained)
Deterministic – discounted					
Scenario 1					
MF (ACI)	6,607	17.8046	-	-	-
ACI (ACI)	20,921	18.5525	14,314	0.7479	19,139
Scenario 2					
MF (MF)	5,015	17.7820	-	-	-
ACI (MF)	19,892	18.5011	14,877	0.7191	20,688

Table 3b: Utility value for no second repair - midpoint value (0.7355)

Procedure	Total mean costs £	Total mean QALYs	Comparison	Incremental costs £	Incremental QALYs	ICER £ (cost per QALY gained)
Deterministic – discounted						
MF (MF)	5,015	17.7820	-	-	-	-
MF (ACI)	6,607	17.8046	MF (ACI) v MF (MF)	1,592	0.0226	70,425
ACI (MF)	19,892	18.5011	ACI (MF) v MF (ACI)	13,285	0.6965	19,074
ACI (ACI)	20,921	18.5525	ACI (ACI) v ACI (MF)	1,029	0.0514	20,020

When altering the utility value of those that "choose not to have a second repair" and using a value same as failure (0.654) the results are similar to the base-case analysis; that is ACI as a first repair is more cost-effective than MF as a first repair; however, the ICERs values have decreased slightly (see Tables 4a showing results by scenario analysis and 4b showing results for all four options).

Table 4a: Utility value for no second repair – same as failure (0.654) by scenario

Procedure	Total mean costs £	Total mean QALYs	Incremental costs £	Incremental QALYs	ICER £ (cost per QALY gained)
Deterministic – discounted					
Scenario 1					
MF (ACI)	6,607	16.3829	-	-	-
ACI (ACI)	20,921	17.5823	14,314	1.1994	11,935
Scenario 2					
MF (MF)	5,015	16.3558	-	-	-
ACI (MF)	19,892	17.5046	14,877	1.1488	12,949

Table 4b: Utility value for no second repair – same as failure (0.654)

Procedure	Total mean costs £	Total mean QALYs	Comparison	Incremental costs £	Incremental QALYs	ICER £ (cost per QALY gained)
Deterministic – discounted						
MF (MF)	5,015	16.3558	-	-	-	-
MF (ACI)	6,607	16.3829	MF (ACI) v MF (MF)	1,592	0.0271	58,622
ACI (MF)	19,892	17.5046	ACI (MF) v MF (ACI)	13,285	1.1217	11,844
ACI (ACI)	20,921	17.5823	ACI (ACI) v ACI (MF)	1,029	0.0777	13,243

When altering the utility value of those that "choose not to have a second repair" and using a value same as success (0.817) the results are similar to the base-case analysis; that is ACI as a first repair is more cost-effective than MF as a first repair; however, the ICERs values are not within the cost-effectiveness threshold (see Tables 5a showing results by scenario analysis and 5b showing results for all four options).

Table 5a: Utility value for no second repair – same as success (0.817) by scenario

Procedure	Total mean costs £	Total mean QALYs	Incremental costs £	Incremental QALYs	ICER £ (cost per QALY gained)
Deterministic – discounted					
Scenario 1					
MF (ACI)	6,607	19.2264	-	-	-
ACI (ACI)	20,921	19.5228	14,314	0.2964	48,293
Scenario 2					
MF (MF)	5,015	19.2083	-	-	-
ACI (MF)	19,892	19.4977	14,877	0.2894	51,413

Table 5b: Utility value for no second repair – same as success (0.817)

Procedure	Total mean costs £	Total mean QALYs	Comparison	Incremental costs £	Incremental QALYs	ICER £ (cost per QALY gained)
Deterministic - discounted						
MF (MF)	5,015	19.2083	-	-	-	-
MF (ACI)	6,607	19.2264	MF (ACI) v MF (MF)	1,592	0.0180	88,182
ACI (MF)	19,892	19.4977	ACI (MF) v MF (ACI)	13,285	0.2713	48,967
ACI (ACI)	20,921	19.5228	ACI (ACI) v ACI (MF)	1,029	0.0251	41,002

III. Separate scenarios around longer term failure rate beyond year 3 (that is, keeping the same utility outlined in (i) but adjusting for differences based on higher failure rates applied to MF i.e. 10% higher, 20% higher etc).

We assume that this request is for a scenario where failure rate is increased but utility is unchanged in those who do not fail, since it would be illogical to keep the same mean utility with higher failure rates?

As we can see from the results below (Tables 6a and 6b), the ICERs are very close to the base-case analysis which was presented.

Table 6a: Long-term failure of MF increased by 10% by scenario

Procedure	Total mean costs £	Total mean QALYs	Incremental costs £	Incremental QALYs	ICER £ (cost per QALY gained)
Deterministic - discounted					
Scenario 1					
MF (ACI)	6,627	17.2702	-	-	-
ACI (ACI)	20,921	18.0228	14,294	0.7526	18,993
Scenario 2					
MF (MF)	5,020	17.2662	-	-	-
ACI (MF)	19,892	17.9805	14,872	0.7142	20,823

Table 6b: Long-term failure of MF increased by 10%

Procedure	Total mean costs £	Total mean QALYs	Comparison	Incremental costs £	Incremental QALYs	ICER £ (cost per QALY gained)
Deterministic - discounted						
MF (MF)	5,020	17.2662	-	-	-	-
MF (ACI)	6,627	17.2702	MF (ACI) v MF (MF)	1,608	0.0040	403,450
ACI (MF)	19,892	17.9805	ACI (MF) v MF (ACI)	13,265	0.7102	18,677
ACI (ACI)	20,921	18.0228	ACI (ACI) v ACI (MF)	1,029	0.0423	24,304

Table 6c: Long-term failure of MF increased by 20% by scenario

Procedure	Total mean costs £	Total mean QALYs	Incremental costs £	Incremental QALYs	ICER £ (cost per QALY gained)
Deterministic - discounted					
Scenario 1					
MF (ACI)	6,645	17.2365	-	-	-
ACI (ACI)	20,921	18.0228	14,276	0.7863	18,155
Scenario 2					
MF (MF)	5,024	17.2289	-	-	-
ACI (MF)	19,892	17.9780	14,869	0.7491	19,850

Table 6d: Long-term failure of MF increased by 20%

Procedure	Total mean costs £	Total mean QALYs	Comparison	Incremental costs £	Incremental QALYs	ICER £ (cost per QALY gained)
Deterministic - discounted						
MF (MF)	5,024	17.2289	-	-	-	-
MF (ACI)	6,645	17.2365	MF (ACI) v MF (MF)	1,621	0.0075	215,595
ACI (MF)	19,892	17.9780	ACI (MF) v MF (ACI)	13,247	0.7415	17,864
ACI (ACI)	20,921	18.0228	ACI (ACI) v ACI (MF)	1,029	0.0448	22,968

5. Clarification of the definition of response applied in economic model.

In our economic model we didn't use the term response. The model was defined by successes and failures.

6. Clarification of the source of cost data used for the first and second procedures. Please explain what the data from Clar et al. (2005) is and where it comes from and the rationale for the most appropriate one for ACI. Background information on the national tariff for day case knee procedures, whether HRG codes actually exist, which codes cover these procedures and what the cost of these is.

Costs of ACI

Table 8 of the PMB reports the costs given in the ChondroCelect submission. The cost for the second procedure, during which the cells are implanted, was £109.65, described as "outpatient setting". This was an error. The cost should have been for a day-case, and has been corrected in the SOBI response to the assessment report, using the figure of £1,033.97 as used in the assessment report. See Table 1, page 3 of the SOBI document.

The £1,033.97 figure is derived by uplifting the costs in the last assessment report by Clar et al (HTA monograph 2005/9/no 47). The costs in that report were derived mainly from Aberdeen Royal Infirmary, supplemented with data from Southampton General Hospital, partly because mosaicplasty was not done in Aberdeen, and partly to check for variations in costs. The main variation noted was that in Aberdeen, microfracture was an inpatient procedure, whereas in Southampton it was a day-case one. After allowing for inflation, these costs were similar to those used in the first NICE appraisal (TA 16, 2000. Details in HTA 2001/5/11).

The Oswestry submission (section 7.1, page 13) gives a cost of £2,398 for the first ACI procedure and £2,396 for microfracture, citing the National Tariff Payment System. (There may be a typo in the £2,938 which should perhaps also be £2,936?). The figure of £2,936 is the cost for HRG HB22C – major knee procedure for non-trauma category 1. This implies a mean inpatient stay of 1.6 days. The NTPS day case tariff for minor knee procedure is HB25F, cost £870.

The Assessment Group thinks the day case cost should be used for arthroscopy with harvesting of chondrocytes.

7. Explanation for why it is appropriate to use the ACI-P and MACI data in the economic model (that is, comments on the comparison of different generations of ACI)

The Warwick model assumes that the outcomes of ACI-C and MACI are similar. The outcome after ACI-P is similar in terms of cartilage repair but hypertrophy is common and so a re-operation to shave off hypertrophied tissue is often needed. In a review of failures and re-operations. Harris et al (reference 29 in assessment report) found unplanned re-operation rates of 27% after ACI-P, 5% after ACI-C and 5% after MACI. For that reason and other reasons (see box 1 of assessment report) ACI-P is now obsolete in the UK.

At one time, it was thought that the periosteal cap acted not just as a cap to protect the cells and keep them in place, but that it might also release growth factors that would encourage the formation by the cells of hyaline cartilage (Nehrer and Brix 2014 – reference 23 in assessment report). A randomised trial by Gooding et al (2006 – reference 21 in AR) showed that there was no advantage in terms of Cincinnati scores at two years, but 36% of the ACI-P group had required shaving of grafts because of hypertrophy by 12 months. The greater need for subsequent

procedures (by day-case arthroscopy) after ACI-P compared to ACI-C makes it more costly and not cost-effective, as reported in the Samuelson study in the assessment report.

One small (21 patients) trial (Zeifang 2010 – reference 55 in AR) that reported that ACI-P gave better results than MACI, was excluded from this review because the matrix used was not collagen.

The Stanmore group (Bartlett et al – reference 54 in AR) also carried out an RCT of ACI-C versus MACI (the Verigen version). Follow-up at 12 months showed improvements in Cincinnati scores in both groups (17.5 and 19.6, p = 0.32). Biopsies showed hyaline-like cartilage or mixed hyaline and fibro-cartilage in 42.9% of the ACI-C group and 36.4% of the MACI group (difference NS), but they were taken in only a proportion of the patients and only at 12 months, before the repairs were fully mature. It should also be noted that at the time of the study, ACI was used only in patients in whom earlier repair procedures had failed, and patients in this study had had an average of 2.2 prior procedures, not including diagnostic arthroscopy, and had long durations of symptoms. Both factors are associated with poorer prognosis.

The TIG/ACT trial used characterised chondrocytes. This development is described in the assessment report, pages 22 and Box 2. There are no RCTs of ACI with characterised chondrocytes versus ACI with uncharacterised chondrocytes. The commercial manufacturers of the products being appraised by NICE use characterised chondrocytes, but the OsCell group does not yet do so. In the ACTIVE trial, two patients received the Tigenix characterised cells.

Matrix-ACI can be performed in two ways. In MACI^{R} the cells come pre-loaded on to the membrane. In the other method, the cells are loaded on to the collagen membrane in theatre and given 10 minutes to adhere before implantation.

8. Comments on the potential importance of subsequent rehabilitation

Rehabilitation is similar after ACI and microfracture. The rehab programmes in trials such as TIG-ACT and SUMMIT are the same for ACI and MF. It is prolonged and patients are advised not to return to previous activities for about 12 months. It is possible that this is a factor in patients who do not have an optimal result and who chose not to have a further repair procedure.

Rehabilitation may need to take longer in patient with high BMI in whom progression to full weight-bearing may need to take longer (Edwards et al 2014). Pre-operative weight loss may be advised.

9. Comments on the potential importance of any subgroups, for example, based on lesion size, duration of symptoms.

As noted in the assessment report, several factors are associated with outcomes;

- ACI is reported to be less successful in patients with BMI > 30 (AR page 153) but numbers of patients with high BMI in the studies were low, and microfracture is also reported to be less successful.

- Duration of symptoms <3 years was reported to be associated with better results in some but not all studies (for example AR pages 14, 26, 35, 38, 70). Vanlauwe et al 2011 reported that results were better with ACI in patients with shorter duration, dividing their patients into < 3 years duration and > 3 years duration of symptoms. However, the mean durations in these two groups for those randomised to ACI were a very short 0.95 years and a rather long 8.4 years respectively. The CCI > 3 year duration group differed from the CCI, 3 years duration in several ways other than duration (> 3 years first): 53% female vs. 29%; 47% abnormal other knee vs. 32%; 100% previous other lesion vs. 79%; acute onset 35% vs. 53%.

- Size of lesion – the advantage of ACI over MF was greater with larger lesions. The outcomes of ACI do not appear to vary by size of lesion except in very large lesions. Minas reported similar results in lesions with areas 1-5cm^2, 5-10cm^2 and 10-15cm^2 with all groups having around 75% graft survival at mean 12 years of follow-up. Lesions with areas > 15cm^2 had only 38% long-term survival but results were often good. In the SUMMIT trial, good responses in patients with lesion size > 4cm^2 were seen in 95% of ACI cases and 77% of MF ones.

- ACI was less successful in patients who had had previous repair attempts but still beneficial. Evidence for this comes from the early trials of ACI where most patients had long duration of symptoms and several previous attempts at repair.

- Age over 50-55 is usually regarded as a contra-indication to ACI, though in one study (Neimeyer 2010), there was no difference in Lysholm score improvements between patients under 40 and those 40 to 57 years.

- The use of ACI in advanced OA is prohibited by licence. This suggests that ACI could be used in early OA and there is some evidence of benefit (see pages 152-3 of AR). However the evidence comes from case series not RCTs.

However, the issue is not whether some factors are associated with better results, but whether any factors or combinations thereof could be used to exclude people from having ACI.

One factor used in the NICE scope to exclude people is absence of symptoms. The Dutch guidelines recommend ACI in asymptomatic knees with grade 5 defects. (Page 152 of AR)

10. A table comparing the utility values from the AG work and the ACTIVE trial

Table 7: Utility values used in the economic model and in the ACTIVE trial sensitivity analysis

	Our economic model		**ACTIVE trial***	
	First repair ACI	**First repair MF**	**First repair ACI**	**First repair MF**
Repairs				
Before primary repair	0.654		0.519	
Successful primary				
1st year	0.760	0.760	0.645	0.627
2nd year	0.817	0.817	0.669	0.667
3rd year	0.817	0.817	0.674	0.673
4th year	0.817	0.817	0.647	0.674
5 years +	0.817	0.654	0.698	0.658
Before second repair	0.654		0.519	
Choose not to have a second repair	0.691*		0.600	

In the absence of data, we assumed that at least some patients choosing not to have a second repair had derived some benefit from the first, and that their mean utility was somewhat better than baseline.

Table 8: Original values from the ACTIVE trial

	Control			ACI		
	Obs	**Mean**	SD	Obs	**Mean**	SD
Baseline	187	**0.532**	0.285	192	**0.506**	0.276
3 month	155	**0.582**	0.28	163	**0.56**	0.252
6 month	155	**0.627**	0.29	169	**0.645**	0.262
1 year	150	**0.675**	0.279	168	**0.636**	0.314
2 year	147	**0.667**	0.301	165	**0.669**	0.29
3 year	140	**0.673**	0.301	163	**0.674**	0.294
4 year	126	**0.674**	0.302	137	**0.647**	0.323
5 year	87	**0.618**	0.313	102	**0.677**	0.321
6 year	75	**0.675**	0.291	80	**0.707**	0.312
7 year	53	**0.705**	0.268	59	**0.735**	0.263
8 year	27	**0.647**	0.272	29	**0.676**	0.33
9 year	5	**0.486**	0.271	2	**0.761**	0.05

11. A table summarising the efficacy data from all trials and technologies

Already provided in assessment report.

12. ICER tables with the correct the results take extended dominance into consideration

Extended dominance was not an issue; hence this was not presented in the ICER tables. The only time dominance was an issue, was in the sensitivity analysis when we used the ACTIVE trial utility values and dominance was take into consideration when the results were presented.