NATIONAL INSTITUTE FOR HEALTH

AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

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

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Response to Assessment Report prepared by Warwick Evidence

Introduction

Having reviewed the assessment report produced by Warwick Evidence assessment group (AG), on most issues Sobi agree with the AG – both in criticisms of the Sobi model and in the conclusions drawn. Sobi are pleased to see that both in their review of the Sobi model and in the Warwick *de novo* model, the same conclusion is reached; ChondroCelect® represents an effective and cost-effective use of NHS resources.

This response contains two main sections

1. Amendments to the Sobi model in response to the criticisms of the AG (where appropriate), including revised results
2. Clarification around where the Sobi model has been misrepresented in the Assessment Report

In this response we have presented two sets of results that incorporate the amendments arising from the AG review as Sobi do not agree with two of the potential amendments. All amendments are related to cost inputs to the model, as the Assessment Report did not challenge clinical model inputs. The Sobi preferred base case incremental cost-effectiveness ratio (ICER) is £8,507, and the AG preferred base case ICER is £8,693. Although both these ICERs are higher than the original ICER of £6,997, they remain highly cost-effective.

Unfortunately, the economic model, which was referred to as attached in the Sobi submission, was omitted from the final communication in error. Although the missing model was not raised by NICE or the AG, the model is provided for the purpose of transparency. Sobi accept, however, that it has been provided too late for the AG to perform a factual accuracy check, nonetheless the data, calculations and sources included will likely aid the AG in revising their own model over time.

Amendments made to the Sobi cost-effectiveness model

The Assessment Report highlights a number of corrections and improvements to the Sobi model. These are described in turn, followed by the updated cost-effectiveness results.

a) Corrections to cost calculations. On page 74 of the Assessment Report, the AG point out that unit costs based upon the Clar et al (2005)[1] study are underestimated as an incorrect base year was used to uplift prices to 2012/13 values. Correctly inflated costs are shown in Table 1. Note that some of these costs, denoted by an asterisk, have been superseded by additional changes made based upon the AG critique.

Table 1: Corrected unit costs based upon Clar et al

Cost item	Original cost	Corrected cost
Arthroscopy*	£722.45	£774.19
Microfracture, inpatient	£2,817.79	£3,019.60
Microfracture, day case	£964.87	£1,033.97
Total knee replacement (TKR)*	£6,500.85	£6,966.44
TKR revision	£12,093.24	£12,959.34
Note: * denotes cost items which are superseded by additional changes to the model.		

b) Arthroscopy and arthrotomy unit costs. The AG suggest that a day case procedure would be required to perform the second stage of the ChondroCelect procedure (page 74 of the Assessment Report). The resulting unit cost used in the Warwick model of £1,033.97 has therefore been applied, replacing the initial arthrotomy cost of £109.65. The new cost was obtained by inflating the unit cost of £804 reported by Clar et al.

The Warwick model utilises a different arthroscopy unit cost from the Clar et al study than the Sobi model. The Warwick model uses the diagnostic arthroscopy cost of £552, uplifted to £709.89. We have therefore also applied this cost for the initial ChondroCelect arthroscopy. This supersedes the arthroscopy unit cost shown in Table 1.

Subsequent debridement and arthroscopy procedures are assumed to incur the arthroscopy ‘with lavage and debridement’ unit cost reported by Clar et al, which is the arthroscopy unit cost shown in Table 1.

c) Knee replacement unit cost. On page 74 of the Assessment Report, the AG state that an NHS reference cost is in fact available for a total knee replacement (TKR) procedure. This is the unit cost for TKR applied in their own model. As such, the Sobi model has been updated to include the same unit cost: £5,676.13 per TKR procedure. This represents the cost of an elective inpatient stay (HRG code HB21C, trauma & orthopaedics)[2]. The revised unit cost supersedes the initial TKR unit cost shown in Table 1.

d) Partial knee replacement. On page 72 of the Assessment Report, the AG note that a first knee replacement can be either a partial replacement (PKR) or a TKR. The Sobi model submitted did not incorporate this possibility, however, we recognised that it may have important cost impacts. Therefore the model has been revised to allow a PKR as the initial knee replacement.

   It appears that the Warwick model assumes an equal likelihood of the first knee replacement being a PKR or TKR, and subsequent procedures must be a TKR. We have therefore made the same assumptions. These have no impact on the first knee replacement cost, which is £5,676.13 irrespective of the procedure. However, 50% of patients who require a second knee replacement will have previously received a PKR. These patients should therefore only incur the cost of an initial TKR for their second procedure (£5,6776.13). The remaining 50% of second replacements will be receiving their second TKR, which incurs the higher cost of £12,959.34. Any patients receiving the third permissible knee replacement must have had at least one TKR previously, and therefore incur the higher procedure cost.

e) Rehabilitation unit cost. The AG state a preference for a different rehabilitation unit cost to the Sobi model, with £256 used in the Warwick model compared to £42.47 in the Sobi model (page 75 of the Assessment Report). The Warwick cost was obtained from NHS reference costs, under the code REHAB2 for joint replacement and appears to be more appropriate. We have therefore revised the Sobi model.

f) Pain relief costs. The Warwick model does not incorporate any cost associated with pain relief medication, as described on page 75 of the Assessment Report. The Sobi model included some pain relief costs, incurred through prescribing non-steroidal anti-inflammatory drugs (NSAIDs) to 50% of patients requiring pain relieving

medication. The cost of NSAIDs is estimated to be £9.79 per month; with a cost of £4.90 per month applied in the model, since NSAIDs are assumed to be given in only 50% of cases.

We maintain that the cost of pain relieving medication is a relevant NHS cost, and that it should be incorporated in the model, though do present results with and without this cost included.

g) Management of unresolved patients. On page 75 of the Assessment Report, the AG assert the unit cost of £384.43 "for some patients … may be an overestimate". While this is undoubtedly true, for some patients this cost may be an underestimate. It is an average cost and is therefore used with the acceptance that some patients will incur lower costs and others will incur higher costs. Although we have presented results with this figure reduced by 25%, we believe the mean cost should be included in the base case.

Table 2 shows the effect of each of the revisions to the Sobi economic model, including also the effect of making changes A-E (with which Sobi agree) to make the preferred Sobi base case, and all changes (A-G) to make the AG preferred case. For the two preferred cases (Sobi and AG), full results are then presented. No individual change makes a substantial difference to the ICER. The Sobi preferred base (revisions A to E) produces an ICER of £8,507, and the ICER with the AG's base case settings is £8,693.

All of the changes made by the AG relate to the costing of the disease, and not to the use of clinical data. As such, the quality-adjusted life years (QALYs) remain constant and equal to the original submission in each scenario: 16.69 with ChondroCelect, 15.40 with microfracture, and 1.29 incremental QALYs. Therefore, these are not shown in Table 2.

Table 2: Revised cost-effectiveness results

Revisions implemented	Treatment	Costs	ICER
Original submission	Microfracture	£13,547	£6,997
	ChondroCelect	£22,586	
	Incremental	£9,040	
Revision A: Corrections to cost calculations	Microfracture	£14,432	£6,637
	ChondroCelect	£23,007	
	Incremental	£8,575	
Revision B: Arthroscopy and arthrotomy unit costs	Microfracture	£14,502	£7,237
	ChondroCelect	£23,852	
	Incremental	£9,350	
Revision C: Knee replacement cost	Microfracture	£13,118	£7,198
	ChondroCelect	£22,417	
	Incremental	£9,299	
Revision D: Partial knee replacement	Microfracture	£12,741	£7,406
	ChondroCelect	£22,309	
	Incremental	£9,568	
Revision E: Rehabilitation unit cost	Microfracture	£13,547	£7,824
	ChondroCelect	£23,655	
	Incremental	£10,108	
Revision F: Pain relief costs	Microfracture	£13,401	£7,064
	ChondroCelect	£22,527	
	Incremental	£9,126	
Revision G: Management of unresolved patients	Microfracture	£13,325	£7,115
	ChondroCelect	£22,518	
	Incremental	£9,193	
Revisions A to E: Sobi preferred base case	Microfracture	£13,631	£8,507
	ChondroCelect	£24,622	
	Incremental	£10,991	
Revisions A to G: AG preferred base case	Microfracture	£13,263	£8,693
	ChondroCelect	£24,494	
	Incremental	£11,231	

Key: AG, assessment group; ChondroCelect, characterised chondrocyte implantation; ICER, incremental cost-effectiveness ratio.

Full model results are provided below for the Sobi preferred base case, and the AG preferred base case.

Table 3: Sobi preferred base case, full discounted results

Model arm	Total			Incremental			ICER
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Microfracture	£13,631	22.88	15.40				
ChondroCelect	£24,622	23.11	16.69	£10,991	0.23	1.29	£8,507
Key: ChondroCelect, characterised chondrocyte implantation; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years.							

Table 4: Sobi preferred base case, disaggregated discounted cost results

Cost item	Microfracture	ChondroCelect	Increment
Procedure (including rehabilitation)	£3,020	£19,024	£16,005
Failure-related rebate	£0	£0	£0
Secondary treatments (MFx, debridement)	£730	£2,124	£1,394
TKR (inc. assessments & revisions)	£8,996	£3,200	-£5,795
Treatment of unresolved patients	£886	£274	-£612
Total costs	£13,631	£24,622	£10,991
Key: ChondroCelect, characterised chondrocyte implantation; MFx, microfracture; TKR, total knee replacement.			

Table 5: AG preferred base case, full discounted results

Model arm	Total			Incremental			ICER
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Microfracture	£13,263	22.88	15.40				
ChondroCelect	£24,494	23.11	16.69	£11,231	0.23	1.29	£8,693
Key: ChondroCelect, characterised chondrocyte implantation; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years.							

Table 6: AG preferred base case, disaggregated discounted cost results

Cost item	Microfracture	ChondroCelect	Increment
Procedure (including rehabilitation)	£3,020	£19,024	£16,005
Failure-related rebate	£0	£0	£0
Secondary treatments (MFx, debridement)	£584	£2,064	£1,481
TKR (inc. assessments & revisions)	£8,996	£3,200	-£5,795
Treatment of unresolved patients	£664	£205	-£459
Total costs	£13,263	£24,494	£11,231
Key: ChondroCelect, characterised chondrocyte implantation; MFx, microfracture; TKR, total knee replacement.			

Sensitivity analysis

In the original submission, the only scenario analysis with a significant impact on the ICER was altering the proportion of patients receiving microfracture as their second procedure. Using the Sobi preferred base case model, applying the same scenario whereby 50% of second-treatment patients on each arm receive a microfracture and 50% receive best supportive measures, the ICER is £28,905. This remains within the range typically considered cost-effective by NICE.

However, it is important to note that this scenario is unlikely to represent clinical practice as expert advice suggests a second microfracture is highly uncommon. If 100% of second-treatment patients receive a microfracture, the ICER is £24,941; again cost-effective, however, we do not feel this treatment sequencing is realistic.

Points of clarification

A number of points are clarified below. Had the Sobi model not been omitted by mistake, many of these clarifications would not have been necessary – responsibility for these corrections needing to be made therefore largely rests with Sobi, and is not a criticism of the AG.

Treatment sequencing

The Assessment Report and Warwick model focus on comparing treatment sequences; for example, comparing ChondroCelect followed by microfracture with microfracture followed by microfracture. The AG take issue with the Sobi model using subsequent microfracture differently between model arms (page 73). However, the use of subsequent microfracture in the Sobi model was informed by the opinion of a clinical orthopaedic expert, who advised that a second microfracture is much less likely to be effective than the first, and is therefore less frequently used. Based upon this advice, patients on the ChondroCelect Sobi model arm are more likely to receive a subsequent microfracture compared to patients on the initial microfracture model arm. We would therefore assert that the Sobi model produces an accurate picture of what would occur in clinical practice, where treatments are unlikely to show the same efficacy when used for a second time.

Additionally, there is limited or no evidence to support a treatment sequencing model (for example, the efficacy of ChrondroCelect following prior ChondroCelect). In a previous NICE Appraisal, TA 319[3], the Committee supported not building a treatment sequence model for this reason.

Furthermore, as noted by the AG, the Sobi model includes sensitivity analysis around the proportion of patients receiving a subsequent microfracture procedure to show the impact of altering this assumption.

Utility values used

On page 75 of the Assessment Report, the same values which were used in the Warwick model, the AG queried the implementation of health-related quality of life in the Sobi model. To clarify, in the Sobi model the utility weight associated with successful surgery is assumed to be maintained while the patient remains in the ‘success’ health state, eroded only by the

age-related population weights over time. That is, utility does not gradually decrease to pre-surgery levels over a given time period.

Applying utilities that decrease gradually in a Markov model with a number of subsequent treatments is inherently difficult due to its memory-less property. Doing so would require the time at which individual patients receive their second procedure to be known, and for each patient to be tracked to ensure the correct utility is being applied only for the correct patients over time. Therefore to retain simplicity, quality of life does not gradually decrease post-surgery.

While we recognise that this is a limitation of the analysis, it should be noted that there is no reason why the rate of decrease in the utility value over time would differ between the ChondroCelect and microfracture model arms. With only a small mortality difference between the two arms (due to death in surgery), it is likely that applying a gradual utility decline would have only a small impact on the ICER. This is supported by the Warwick model, which incorporates such a decline and still estimates ChondroCelect to be cost-effective.

Role of gender in the model

On page 72 of the Assessment Report, the AG describe the Sobi model as being *"separated by gender"*. The reason for this is questioned, as a patient's gender has no bearing on the efficacy of the procedures under consideration, all else equal.

The proportion of male or female patients does not affect the efficacy of any treatment in the model, and as the AG correctly identify, nor should it. Gender only has an effect in the background mortality calculations, as the life tables show differential mortality between males and females. This should be taken into account when estimating an overall background mortality rate, using the gender profile of the anticipated patient population.

As males have a higher background mortality rate, over time the population profile will become increasingly female and the rate will converge towards to the female rate.

Number of knee replacements permitted

On page 72 of the Assessment Report, the AG make the following two statements: *"The submission model assumes that a patient can only receive up to a maximum of three TKRs."* And *"If the second TKR fails then the patients receives just analgesics."*

These statements appear to contradict one-another. We would like to clarify that the first statement is correct, in that up to three TKRs are permissible in the Sobi model. This is in line with the Warwick model. The second statement appears to be a misunderstanding by the AG. Following the failure of a second TKR, patients are assessed for their third replacement. If they are determined to be unsuitable, or if this third TKR fails, patients then go on to receive pain relieving medication and become unresolved cases.

The second statement would be correct if it said *"If the second TKR revision fails…"* as the second revision would, in effect, be the third and final TKR.

References

[1] Clar C, Cummins E, McIntyre L, et al. Clinical and cost-effectiveness of autologous chondrocyte implantation for cartilage defects in knee joints: systematic review and economic evaluation. *Health Technol Assess*. 2005; 9(47):iii-iv, ix-x, 1-82.

[2] National Health Service. Department of Health Reference Costs 2012-13. 2013. Available at: https://www.gov.uk/government/publications/nhs-reference-costs-2012-to-2013 Accessed: 5 January 2015.

[3] National Institute for Health and Care Excellence. Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma. 2014. Available at: http://www.nice.org.uk/Guidance/ta319 Accessed: 6 January 2015.