Public observer slides – no AIC information

Lead team presentation

Autologous chondrocyte implantation with chondrosphere for treating articular cartilage defects [ID851]

1st Appraisal Committee meeting

Committee B

Chair: Sanjeev Patel

Lead team: Ray Armstrong, John Cairns, Nigel Westwood

ERG: Warwick Evidence

NICE technical team: Sharlene Ting, Jasdeep Hayre

16th November 2017

Summary of evidence

Clinical effectiveness

<u>COWISI randomised controlled trial results at 2 years</u>

- chondrosphere *vs* microfracture: [redacted]

<u>Network meta-analysis results up to 3 years</u>

- No statistically significant differences in outcomes seen for chondrosphere vs other treatments (2nd and 3rd generation ACI and microfracture)

Cost effectiveness

<u>Incremental cost-effectiveness ratios (ICERs) for base case</u>

- Company (lifetime horizon): chondrosphere → microfracture vs microfracture → microfracture: **£4,051/QALY**
- ERG (lifetime horizon): chondrosphere → microfracture vs microfracture only: **£4,949/QALY**

ACI Autologous chondrocyte implantation, ERG Evidence review group, ICER Incremental cost effectiveness ratio, KOOS Knee injury and osteoarthritis score, QALY Quality adjusted life year

Key issues – decision problem and clinical evidence

- How are articular cartilage defects currently treated in the NHS?
  - What determines treatment choice?
- Is chondrosphere a clinically effective treatment?
  - If so, for any lesion size?
- Are all relevant comparators included in the submission?
  - Company does not include traditional ACI
- Main study (COWISI) is a non-inferiority trial comparing chondrosphere with microfracture
  - Is COWISI generalisable to NHS clinical practice?
  - Are the findings robust? [redacted]
- Chondrosphere is compared with 2nd and 3rd generation ACI techniques in a network meta-analysis
  - Are the studies sufficiently similar to be pooled?
  - Are the estimates from the network meta-analysis valid?

ACI Autologous chondrocyte implantation, KOOS Knee injury and osteoarthritis score

Key issues – cost effectiveness

- Are the modelled treatment pathway and treatment sequences appropriate?
- Which treatment sequences are clinically relevant and most appropriate for decision making?
- How should treatment effectiveness estimates be calculated and applied in the model?
- How should transition probabilities be derived?
- Which base case is preferred: company's or ERG's?
- Is chondrosphere an innovative treatment?
  - Are there any benefits not captured in the modelling?
- Equality issues

Chondrosphere
(Spherox, co.don)

MARKETING AUTHORISATION
"Repair of symptomatic articular cartilage defects of the femoral condyle and the patella of the knee (International Cartilage Repair Society [ICRS] grade III or IV) **with defect sizes up to 10 cm^2 in adults**"

Composition and mechanism of action

To make spheroids, healthy cartilage is taken from the patient's joint and grown in the laboratory over 6-8 weeks. The spheroids are implanted evenly into the defect site, which stick without fibrin glue or cover flap. The spheroids repair the defect with healthy cartilage over time

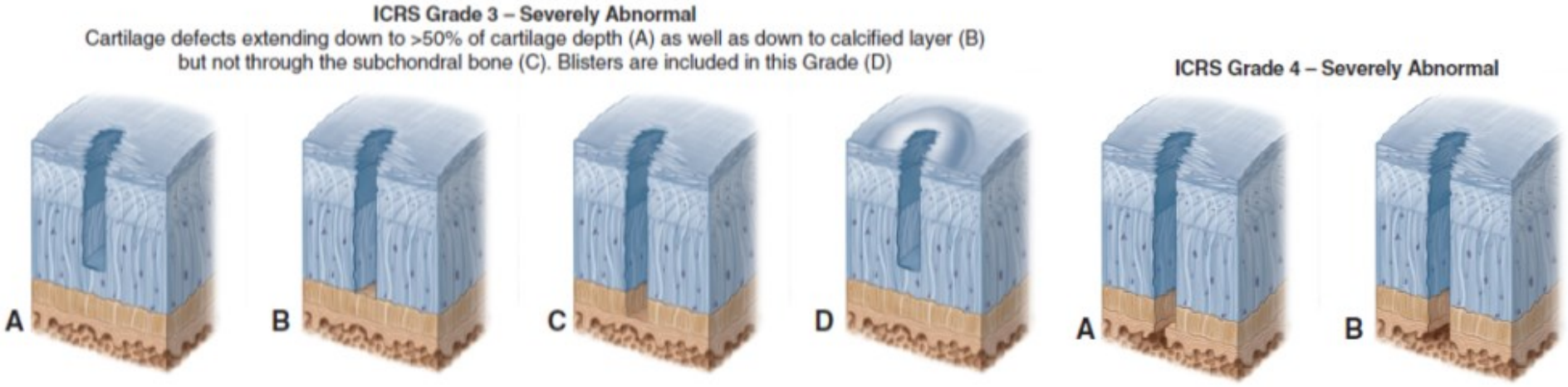
Administration and dose

10-70 spheroids/cm^2 defect in pre-filled syringe or applicator. Matrix-associated autologous chondrocyte implantation (MACI) via arthroscopy or mini-arthrotomy

Disease background: articular cartilage defects

- Articular cartilage: smooth lubricated surface for joints
- Does not have blood vessels or nerves
- Limited capacity for healing and repair
- Can lead to long-term joint problems such as osteoarthritis
- Mechanism of injury: trauma, wear and tear, knee instability, abnormal unbalanced pressures, obesity leading to excessive weight bearing, post-sepsis, osteochondritis dissecans

International Cartilage Repair Society Grade III and IV cartilage lesions



Autologous chondrocyte implantation (ACI)

Generations of ACI	NICE recommendation
Generation: 1st (ACI-P) Cultured chondrocytes placed in defect and covered with a cap made from periosteum	Recommended in TA477
Generation: 2nd (ACI-C or ACI-M) Cultured chondrocytes placed in defect and covered with a collagen cap or matrix cap Technologies: “traditional ACI“ OsCells (hospital exemption); ChondroCelect (not currently licensed)	
Generation: 3rd (MACI) Cultured chondrocytes are seeded to a membrane or “scaffold” Technology: MACI® Vericel (not currently licensed)	
Generation: 4th Does not use flap, membrane or scaffold Technology: chondrosphere (currently licensed)	Current appraisal

ACI-C/P/M Autologous chondrocyte implantation – cap/periosteum/matrix

Best supportive care (conservative management)
physiotherapy, corticosteroid injections, pain medication, weight loss

Reparative/restorative procedures
knee lavage ± debridement, microfracture, mosaicplasty, ACI
Considerations: patient-related factors (surgical history, age, body mass index), lesion (condition, size)

Mosaicplasty or other ACI if symptoms persist after MF or ACI

Osteotomy, knee replacement for larger lesions or if osteoarthritis develops

IPG162 recommends mosaicplasty under special arrangements for clinical governance, consent and audit or research.

TA477 recommends ACI for symptomatic articular cartilage defects of the knee, only if:

- person has not had previous surgery to repair articular cartilage defects
- there is minimal osteoarthritic damage to the knee
- the defect is over 2cm^2 and
- the procedure is done at a tertiary referral centre

ACI: Autologous chondrocyte implantation
MF: Microfracture

Best supportive care

Patient and professional feedback

- No submissions from patient and professional organisations were received

Decision problem – comparators

Company only includes microfracture and ACI (excluding traditional ACI)

ERG: considers ACI (excluding traditional ACI) is only relevant comparator given the recommendation in TA477

NICE scope	Company submission and rationale
As appropriate for lesion size: • Microfracture (marrow stimulation) • Autologous chondrocyte implantation [now published as TA477, ACI recommended] • Knee debridement • Mosaicplasty • Best supportive care (non-operative intervention)	**Include** • Microfracture – most widely used in NHS • ACI – ChondroCelect and VeriMACI **Exclude** • Traditional ACI – available at 1 NHS centre • Knee debridement – used before or after ACI or microfracture • Mosaicplasty – used when symptoms persist after ACI or microfracture • Best supportive care – conservative management offered before surgery

ACI: autologous chondrocyte implantation; MACI: matrix-induced chondrocyte implantation, MF: microfracture

❖ ***Where would chondrosphere fit in the treatment pathway?***

❖ ***What are the most appropriate comparators?***

Primary outcome measure: Knee Injury and Osteoarthritis Score (KOOS)

- 5 subscales: pain, symptoms, activities of daily living, sport and recreation function, knee-related quality of life
- Overall score: mean of 5 subscales
- Normalized score: 100 (no symptoms) to 0 (extreme symptoms)
- Minimal clinically important difference: 8 to 10 points
- Responders reported at 2 levels:
  - achieving at least 8 point improvement in overall KOOS from baseline
  - achieving at least 10 point improvement in overall KOOS from baseline

Clinical evidence for chondrosphere

Randomised controlled trials

- **Phase 3 COWISI – used in health economic model** (chondrosphere *vs* microfracture; **lesion sizes 1-4cm^2**)
- ***Phase 2 – dose-finding study*** *(chondrosphere: low 3-7 vs medium 10-30 vs high 40-70 spheroids/cm^2;* ***lesion sizes 4-10cm^2*** *)* – ***not used in economic modelling***

Network meta-analysis

ACI (chondrosphere, chondrocelect, VeriMACI), microfracture

COWISI and Phase 2: Study characteristics

	COWISI (n=102) Chondrosphere vs microfracture (mean dose 25±16; 7-70 spheroids/cm^2 at implantation)	**Phase 2 (n=75) Chondrosphere: low 3-7 vs medium 10-30 vs high 40-70 spheroids/cm^2**
Year	Dec 2010 to Dec 2020	Oct 2010 to Nov 2017
Design: multicentre, open-label, parallel arm trials	Phase 3, 1:1 randomised (centralised; stratified: age 18-34, >35 years), **non-inferiority** (margin 8.5 overall KOOS)	Phase 2, 1:1:1 randomised (stratified: cartilage defect 4-6.99, 7-10cm^2)
Centres	9 in Germany, 3 in Poland	10 in Germany
Population: adults (18-50 years), ICRS grade III or IV single defect	on femoral condyle	on femoral condyle, trochlea, tibia, retropatellar. Osteochondritis dissecans
Key inclusion/exclusion	no defects in both knees, instability, misalignment >5^o; no comorbidity/previous ACI/mosaicplasty/meniscal implant or recent suture/50% resection of meniscus or incomplete meniscal rim in affected knee; no microfracture in past year; no rheumatoid or para/infectious arthritis, pregnancy or BMI >30kg/m^2	
Defect size after debridement:	1 to 4cm^2 and 6mm depth No osteochondritis dissecans	≥4 to 10 cm^2 and 6mm depth
Follow up: year 1, 2, 3, 4 and 5	Primary outcome at Year 2	Primary outcome at Year 1

COWISI and Phase 2: Baseline characteristics

ERG: COWISI baseline characteristics between groups are similar

	COWISI			Phase 2
	Chondrosphere (n=52)	**Microfracture (n=50)**	**Total (n=102)**	**Total (n=75)**
Male	63%	56%	60%	[redacted]
Age (years)*	36 ± 10	37 ± 9	37 ± 9	[redacted]
BMI (kg/m^2)*	25.7 ± 3.3 (18.8 to 31.2)	25.8 ± 3.0 (18.2 to 30)	25.8 ± 3.1 (18.2 to 31.2)	[redacted]
Smokers	27%	40%	33%	[redacted]
Post-debridement lesion size*	2.7 ± 0.8 (1.4 to 5.0)	2.0 ± 0.8 (0.8 to 4.0)	NR	[redacted]
Primary defect location	100% femur	98% femur 2% patella	99% femur	[redacted]
Traumatic knee defect	37%	48%	42%	[redacted]
Baseline KOOS*	56.6 ± 15.4	51.7 ± 16.5	NR	57 ± 15.2

*Mean ± standard deviation (range where applicable), BMI: body mass index, KOOS: knee injury and osteoarthritis score, NR: not reported

COWISI: quality assessment

ERG: good quality trial, risk of bias from lack of blinding, non-inferiority margin not adequately justified

- **ERG quality assessment:** overall good quality
- Non-inferiority rather than superiority design
  - Non-inferiority margin of 8.5 KOOS points
    - **Company:** previous trial (2008) used 9.0. Research suggests minimal clinically important difference for KOOS ranges from 8 to 10 points
    - **ERG:** inadequately justified in terms of other possible benefits that counteract loss of efficacy
- Generalisability
  - **Company:** COWISI generalisable to UK NHS patients

- ***Is the COWISI population representative of NHS patients with articular cartilage defects?***
- ***What is an acceptable non-inferiority margin for the Knee Injury and Osteoarthritis Score (KOOS)?***

KOOS Knee injury and osteoarthritis score

COWISI – KOOS results

[redacted]

Outcome at 2 years	Chondrosphere (n=48)	Microfracture (n=49)
Change from baseline in overall KOOS (mean ± SD)*[ab]	[redacted]	[redacted]
Responders (≥8 point improvement in KOOS)	[redacted]	[redacted]
Responders (≥10 point improvement in KOOS)	[redacted]	[redacted]

*KOOS sub-scores had the same qualitative result as overall KOOS. [redacted]

[a]Baseline refers to pre-implantation for chondrosphere or pre-microfracture

[b]Repeated measures ANCOVA ([redacted], $p<0.0001$, lower bound [redacted]), ANOVA (6.2), Satterthwaite test ([redacted], $p=0.0003$, lower bound [redacted])

KOOS Knee injury and osteoarthritis score, SD standard deviation

COWISI – KOOS results for post hoc subgroup analysis for defect size

[redacted]

Outcome at 2 years (mean ± SD)	Defect size 1-2cm²		Defect size >2-4cm²	
	Chondrosphere (n=[redacted])	Microfracture (n=[redacted])	Chondrosphere (n=[redacted])	Microfracture (n=[redacted])
Change from baseline in overall KOOS (median [IQR])	[redacted]	[redacted]	[redacted]	[redacted]
Non-inferiority test (least square mean difference; t-test)		[redacted]		[redacted]

- ***Does lesion size affect the clinical effectiveness of chondrosphere?***
- ***Is chondrosphere effective in lesion sizes 1-2cm²?***

[CI]Confidence interval, [IQR]Interquartile range, [KOOS]Knee injury and osteoarthritis score, [SD]standard deviation

Phase 2 (lesion size >4 to 10cm^2) – KOOS results

[redacted]

Mean ± SD change from baseline in overall KOOS at	Low dose (3-7 spheroids/cm^2) (n=24)	Medium dose (10-30 spheroids/cm^2) (n=25)	High dose (40-70 spheroids/cm^2) (n=24)	Total (n=73)
1 year	[redacted]	[redacted]	[redacted]	[redacted]
2 years	[redacted]	[redacted]	[redacted]	[redacted]
3 years	[redacted]	[redacted]	[redacted]	[redacted]
4 years	[redacted]	[redacted]	[redacted]	[redacted]

Pre-planned subgroup analyses on diagnosis (traumatic cartilage lesion, osteochondritis dissecans

❖ ***Is chondrosphere effective in lesion sizes >4 to 10cm^2?***

KOOS Knee injury and osteoarthritis score, SD standard deviation

Phase 2 study

- Key design issues
  - uncontrolled dose ranging study
  - mutually exclusive patient type to COWISI
  - Long term follow up at 4 years

- ***Can the data from the COWISI trial (lesion size 1 to 4 cm^2) be extrapolated to lesion sizes ranging from >4 to 10 cm^2?***
- ***Is chondrosphere a clinically effective treatment compared to microfracture?***

ERG comments on long term effectiveness of ACI

- COWISI showed [redacted] between chondrosphere and microfracture at 2 years
  - Similar results were reported at 5 years for traditional ACI and microfracture (ACTIVE trial – OsCells)
  - Benefit of ACI is likely to be seen over longer term (TA477 observational studies)
  - Clinical effectiveness observed in TIG/ACT (ChondroCelect) and SUMMIT (VeriMACI) trials may be explained by the differences in patient characteristics

❖ ***Is chondrosphere likely to show long-term benefit?***

ACI Autologous chondrocyte implantation

Network meta-analysis – Characteristics of included studies (1)

ERG: studies are different in location, study period and duration of symptoms

	COWISI Chondrosphere, CHS		TIG/ACT ChondroCelect, CC		SUMMIT VeriMACI	
Location	12 centres in 2 EU countries		13 centres in 4 EU countries		16 centres in 7 EU countries including UK	
Study period	Dec 2010-ongoing (2 years)		Feb 2002 to Jan 2008 (2 years)		May 2008 (5 years)	
Comparison	CHS n=52	MF n=50	CC n=57	MF n=61	VeriMACI n=72	MF n=72
Age (years)*	36 ± 10	37 ± 9	33.9 ± 8.5	33.9 ± 8.6	34.8 ± 9.2	32.9 ± 8.8
Men (%)	64	56	61	67	63	67
BMI (kg/m²)*	25.7 ± 3.3	25.8 ± 3.0	46% BMI 25-30	39% BMI 25-30	26.2 ± 4.3	26.4 ± 4.0
Duration of symptoms (years)	[redacted]	[redacted]	1.97	1.57	5.8	3.7

Network meta-analysis – Characteristics of included studies (2)

ERG: VeriMACI had larger lesions, higher rates of previous microfracture and greater disease burden

	COWISI (Chondrosphere, CHS)		TIG/ACT (ChondroCelect, CC)		SUMMIT (VeriMACI)	
Comparison	CHS n=52	MF n=50	CC n=57	MF n=61	VeriMACI n=72	MF n=72
Lesion type	ICRS grade III and IV single femoral condyle defect		Symptomatic single grade III to IV femoral condyle defect		Medial/lateral femoral condyle ± trochlea defects; Outerbridge grade III or IV, OCD if no bone graft needed	
Lesion size (cm^2)	2.2 ± 0.7	2.0 ± 0.8	2.6 ± 1.0	2.4 ± 1.2	4.9 ± 2.8	4.7 ± 1.8
Medial location	100%	98%	100%	100%	75%	74%
Previous knee repair	None		14%	7%	35% marrow stimulation	
Baseline overall KOOS	56.6 ± 15.4	51.7 ± 16.5	56.3 ± 13.6	59.5 ± 14.9	NA	NA
Baseline KOOS pain subscore	63.8 ± 18.5	58 ± 18.3	62.1 ± 18.73	65.5 ± 17.1	37 ± 13.5	35.5 ± 12.1

MF: microfracture, OCD: osteochondritis dissecans

Network meta-analysis – Characteristics of included studies (3)

ERG: studies are different in outcome definitions and assessment time points

	Treatment response (improvement from baseline)	Treatment failure	Time point
COWISI (Chondrosphere)	≥10 improvement in overall KOOS	Objective clinical findings and worsening of overall KOOS and subdomains: need for revision surgery	2 years
TIG/ACT (ChondroCelect)	≥10 improvement in overall KOOS ± ≥10 improvement in ≥3 KOOS subdomains ± improvement in knee disorder severity ≥1 category or decrease of ≥20 points in VAS pain score ± improvement in knee disorder severity ≥1 category	Persistent or recurrent symptoms: re-intervention needed	3 years
SUMMIT (VeriMACI)	≥10 improvement in both KOOS pain and function subscales	Global assessment same or worse than at baseline, <10% improvement in KOOS pain, physician diagnosed failure ruling out all other causes: need for surgical retreatment	2 years

Network meta-analysis – Validity

ERG: "do not regard the results of the NMA as robust, and insufficient to support the cost-effectiveness analysis"

- Uncertain if trials are comparable. Company's qualitative assessment:
  - Mean lesion sizes is larger in SUMMIT (>4cm^2) than in COWISI and TIG/ACT (<2.5cm^2)
  - SUMMIT moderate to severe KOOS pain subscores indicate more severe disease (<55) at baseline than COWISI and TIG/ACT
  - Follow up in COWISI and SUMMIT is shorter (2 years) than in TIG/ACT (3 years)
- ERG agrees. Studies are different in:
  - lesion size, previous knee repairs, baseline KOOS (can affect treatment results)
  - time periods and settings (variation in microfracture techniques)
  - Outcome definitions and assessment timepoints

❖ ***Are the studies sufficiently similar to be pooled?***

Network meta-analysis – Results

No differences in response and failure rates between chondrosphere and microfracture or ACI up to 3 years

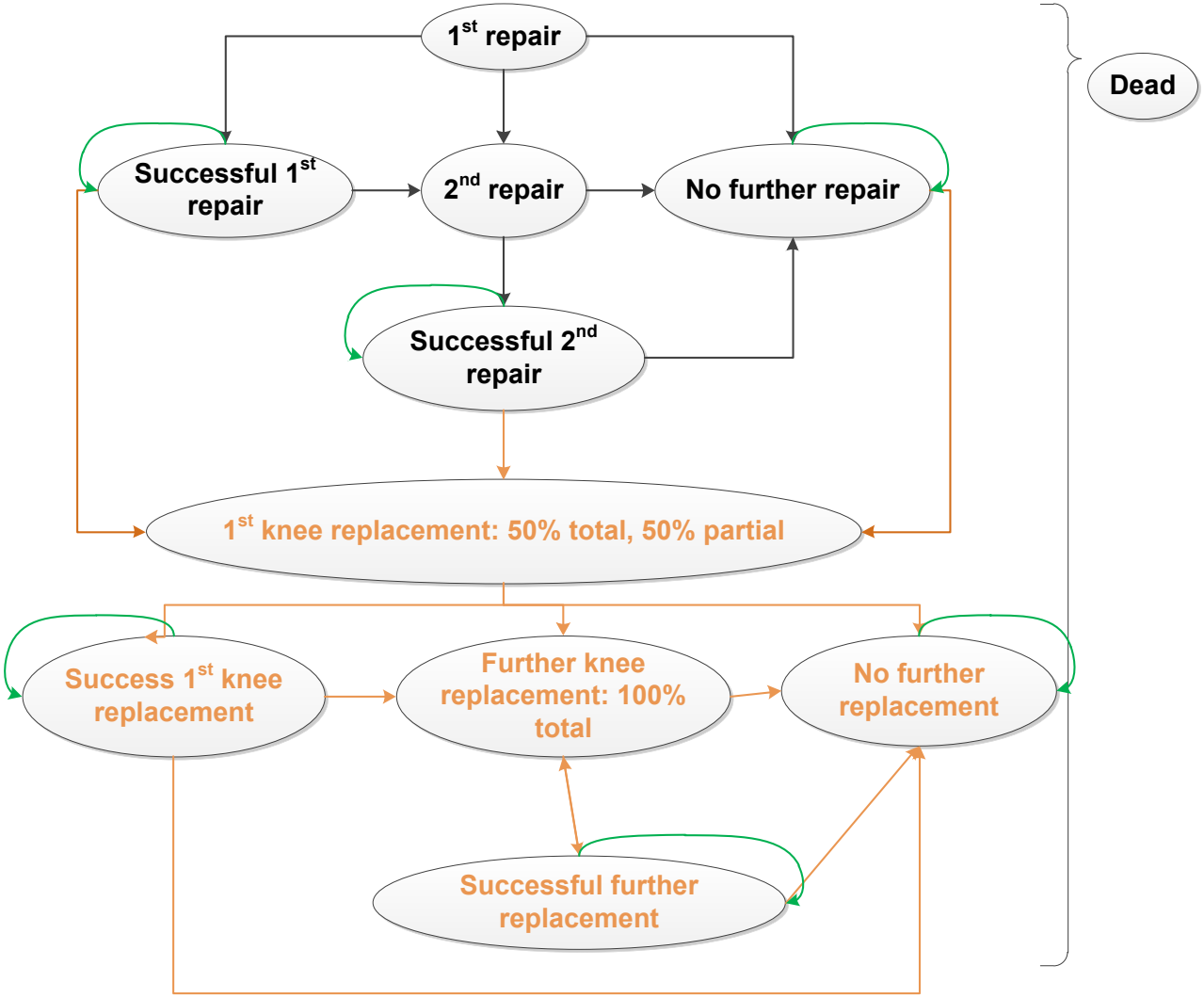
Comparisons	Median relative risk, 95% credible intervals	
	Responders*	Failure rates*
Chondrosphere: higher responders and lower failure rates than microfracture	0.97 (0.79, 1.46)	6.98 (0.37, 3,363)
Chondrosphere: fewer responders and lower failure rates than ChondroCelect	1.22 (0.93, 1.86)	2.03 (0.06, 1,087)
Chondrosphere: fewer responders and same failure rates as VeriMACI	1.22 (0.96, 1.88)	0.99 (0, 798.10)

*All results are not statistically significant

- ***Is chondrosphere clinically effective compared to 2nd and 3rd generation ACI?***
- ***Are the results from the network meta-analysis robust?***

Cost effectiveness

Company model – Structure



Model structure: up to 55 years; over 55 years

- Markov model based on TA477
- Lifetime horizon (67 years)
- Annual cycle
- Population characteristics: 60% male, mean age 33 years
- NHS/PSS perspective
- 3.5% discount rate
- 10 sequences of 2 treatments (treatment 1: all patients; treatment 2: people needing repairs after treatment 1)
- **Assumption: all successful with microfracture return to baseline utility values at 5 years**

Company model – treatment sequences

Sequences	1st repair (all patients)	2nd repair (only people needing repairs after treatment 1)	Proportion of people receiving 2nd repair (annual probabilities)		
			Company	TA477	ERG
Microfracture → microfracture	microfracture	microfracture	0.86%	4%	0%
Microfracture → ACI	microfracture	Chondrosphere ChondroCelect VeriMACI	0.86% 0.86% 0.86%	4% 4% 4%	1.76% 1.76% 1.76%
ACI → microfracture	Chondrosphere ChondroCelect VeriMACI	Microfracture	0%* 1%^ 0%*	1.3% 1.3% 1.3%	0%* 1%^ 0%*
ACI → ACI	1st and 2nd repair are assumed to be the same Chondrosphere → Chondrosphere ChondroCelect → ChondroCelect VeriMACI → VeriMACI		0%* 1%^ 0%*	1.3% 1.3% 1.3%	0%* 1%^ 0%*

ACI: autologous chondrocyte implantation

*0% for 1st year. After 1st year, probability is 0.63%

^2 year probability of response and failure applied during the 1st cycle

Company model – treatment sequences
ERG comments

- 2nd microfracture unlikely if 1st microfracture is not successful (TA477)
- TA477 recommends ACI for people with no previous knee repair surgery
- Relevant comparators are:
  - microfracture only
  - ACI→microfracture
  - ACI→ACI

❖ ***Is the modelled treatment pathway clinically appropriate?***
❖ ***Which treatment sequences are most clinically relevant?***

Company model – Health states (1)

Health state	Company description
1st repair	Can be microfracture or any ACI. Move to successful 1st repair, 2nd repair or no further repair
No further repair	No further repairs. On pain medication and can receive knee replacement after 55 years
Successful 1st repair: states can be permanent or temporary	Permanent: patients stay in successful 1st repair state Temporary: repair fails after being symptom free for years. Can decide to have 2nd repair ERG: main structural difference between chondrosphere model and TA477 model. TA477 allows successful 1st repair to move to no further repair
2nd repair	Only people needing 2nd repair receive one. Options are: MF→MF, MF→ACI, ACI→MF, ACI→ACI. Move to successful 2nd repair or no further repair
Successful 2nd repair: states can be permanent or temporary	Permanent: patients stay in successful second repair state Temporary: no further repair

Company model – Health states (2)

Health state	Company description
1st knee replacement (KR)	At 55 years, patients can receive a knee replacement (50% total or 50% partial*). Move to successful 1st KR, further KR or no further KR
Successful first knee replacement	Permanent: no further KR Temporary: further KR
No further KR	Patients choose not to receive further KR and stay in this state until they die
Further KR	100% total KR. Can move to successful further KR or no further KR. No limit on number of KRs
Successful further KR	Permanent: patients stay for rest of life Temporary: have another KR, no further KR. No limit on number of KRs
Death	Absorbing health state

*Assumption from TA477

ERG comments on model structure

- Model structure up to 55 years
  - Main structural difference from TA477: company model does not allow movement from successful 1st repair to no further repair; only to a 2nd repair
    - All successful 1st repairs remain successes until 55 years, after which a small proportion receive knee replacements each year
  - Overstates treatment benefits for ACI compared with TA477 model (see table)
    - transition from a 1st repair success (QoL=0.817) to no further repair (QoL=0.691)

	Company model – this appraisal		1st AG report (MTA TA477)		3rd AG report (MTA TA477)[a]	
	Costs	QALYs	Costs	QALYs	Costs	QALYs
MF->ACI	£7,608	15.966	£6,607	17.028	£6,248	17.135
ACI->ACI	£21,636	18.098	£20,921	18.023	£22,461	17.995
Net	£14,028	2.131	£14,314	0.994	£16,213	0.860
ICER	**£6,186**		**£14,395**		**£18,844**	

ACI: autologous chondrocyte implantation; AG: assessment group; ICER: incremental cost effectiveness ratio; MF: microfracture; QALY: quality adjusted life year

[a]Differs from original model in 1st AG report: applies time-to-event data on loss of response and the costs of harvesting to £870 and the costs of implantation to £2,396

Company model
Inputs: Clinical effectiveness data (1)

- Assumption: effectiveness of 1st repair = effectiveness of 2nd repair
- Company models treatment effectiveness using response rate data from COWISI and associated relative risks from network meta-analysis.
- These values were used to inform the transition probabilities for the different repair health states (model structure up to 55 years)
  - ERG comments:
    - did not agree with calculation methods
    - Different microfracture response rates within trials may result in too high an estimate for ChondroCelect and VeriMACI
    - **Scenario analysis:** pooled microfracture response data across the 3 trials to yield an estimate of 70% and used the company NMA to provide estimate of 72% for chondrosphere, 88% for VeriMACI and 87% for ChondroCelect

Company model

Inputs: Clinical effectiveness data (2)

- Assumption: effectiveness of 1st repair = effectiveness of 2nd repair
- These values were used to inform the transition probabilities for the different repair health states (model structure up to 55 years)

	Chondrosphere	Microfracture*	ChondroCelect*	VeriMACI*
First 2 years (trial period)				
2nd repair needed (failure rate)	[redacted]	3.4%	1%	0%
Response rate	[redacted]	80% [ERG: 78.4%]	87% [ERG: 97.9%]	87% [ERG: 99.1%]
Non-response rate	[redacted]	20%	13%	13%
Subsequent years (cycle adjusted trial probabilities)				
2nd repair needed (failure rate)	1.25%^	1.72% [ERG: 1.73%]	1.25%^	1.25%^
Response rate	90%	89%	93%	93%
Non-response rate	10%	10.6%	6.7%	6.8%

*data obtained by applying the relative risk from the NMA to the response rate for chondrosphere from COWISI. ^Failure rates not extrapolated from trial; assumed from TA477.

Corrected ERG values in its exploratory analysis

Company model
Inputs: Clinical effectiveness data (3)

Treatment response (success) for 2nd repairs (independent of type of 1st repair)

Company: used 1 year probability of response by taking the square root of the 2 year probability e.g. √response rate for chondrosphere from COWISI

ERG: company only applies the square root once. Every patient that gets a 2nd repair has this 2nd repair probability of response applied once. Company does not compound over 2 model cycles. Overestimates successes, bias in favour of ChondroCelect and VeriMACI and against microfracture.
Exploratory analysis: Apply 2 year probability of response in 1 model cycle

Response rates for 2nd repairs			
Chondrosphere	ChondroCelect	VeriMACI	Microfracture
[redacted] [ERG: [redacted]]	93% [ERG: 96.5%]	93% [ERG: 96.5%]	89% [ERG: 94.5%]

Company model
Transition probabilities (repair health states, up to 55 years)

	Company input and/or calculations	ERG comments
Staying in successful 1st repair	Permanent success: 100% – probabilities of other health states Unsuccessful repair: temporary success, 2nd repair, no further repairs until total knee replacement (0.0063)	-
Successful 2nd repair to no further repair	Non-response rate	Does not use failure rates Use probability of 1st repair of same type
Staying in successful 2nd repair	1 – non-response rate	-

Company model
Inputs: Utility values for repairs

- Assumption: all successful microfracture fail completely at year 5 and return to baseline QoL. **Company and ERG scenario analysis: QoL maintained at 0.817 (key driver in model and issue in TA477)**

	Successful 1st repair		Successful 2nd repair		
	ACI	MF	ACI after ACI	ACI after MF	MF
Year 1	0.760	0.760	0.760	0.760	0.760
Year 2	0.817	0.817	0.817	0.817	0.817
Year 3	0.817	0.817	0.817	0.817	0.817
Year 4	0.817	0.817	0.817	**0.789^**	0.817
Years 5+	0.817	**0.654***	0.817	0.789	0.654

1st or 2nd repair → no further repair: QoL 0.691
Need 2nd repair: QoL 0.654
*All successful MF fail completely at year 5: baseline QoL
^ACI worsens at year 4 to midpoint of 1st year QoL and QoL of success

Derived from TA477 (Gerlier 2010)
ACI: autologous chondrocyte implantation (can be chondrosphere, ChondroCelect or VeriMACI); MF: microfracture

❖ ***How should treatment waning for microfracture be modelled?***

Company model
Inputs: Utility values for knee replacements

	1st knee replacement	Further knee replacement
Success	0.780	0.780
Knee replacement to no further replacement	0.691	0.557*
Successful knee replacement to no further replacement	0.557*	0.557*

1st knee replacement received: QoL 0.615
Further knee replacement received: QoL 0.691
*ERG: TA477 applies 0.691. Lower utility disadvantages sequences that result in more knee replacements
In company clarification response, it states that it corrected the utility values and applied 0.691 to all knee replacement to no further replacement health states

Derived from TA477 (Dong 2006, Gerlier 2010, Jansson 2011)

❖ ***Which utility values are preferred?***

Company model
Inputs: Resources and costs

	CHS	CC	VeriMACI	MF	1st P/TKR and TKR after PKR	Further KR
Cost of cells	£10,000	£16,000^	£16,000	-	-	-
Harvesting	£734[a]	£734[a]	£734[a]	-	-	-
Implantation	£734[a]	£1,065[b]	£1,065[b]	-	-	-
Procedure	..	..	..	£3,122[c]	£5,566[d]	£13,397[e]
Procedure cost	£11,468	£17,799	£17,799	£3,122	£5,566	£13,397
Outpatient visit[f]*	6	6	6	3	2	2
Rehabilitation visit[f]	3	3	3	3	0	0
Total Cost (1 cycle)	£13,226	£19,556	£19,556	£4,518	£5,807	£13,638

[a]**Source:** Arthroscopy (TA477) **ERG**: TA477 FAD preferred £870

[b]**Source:** Arthrotomy (TA477) **ERG**: TA477 FAD preferred £2,396

[c]**Source:** Microfracture (TA477)

[d]**Source:** 2016/17 National Prices and Tariff. **ERG**: NHS reference costs not used. Broadly in line with unadjusted (for inflation) costs in TA477 (£5,676). Model not sensitive to cost of knee replacements

[E] **Source:** 2nd total knee replacement (TA477)

[F] **Source:** NHS reference cost of £345

***ERG:** Incorrect cost applied; paediatric trauma/orthopaedics of £121 vs trauma/orthopaedics of £110

^**ERG**: Confidential discount is available for technology

CC: ChondroCelect, CHS: Chondrosphere, MF: Microfracture; P/TKR: partial/total knee replacement

Company model – base case deterministic, fully incremental results

	Cost	QALYs	Δ Cost	ΔQALYs	ICER
MF→MF	£5,762	15.878	-	-	-
MF→chondrosphere	£7,152	15.944	-	-	ext. dominated
MF→ChondroCelect	£8,162	15.951	-	-	ext. dominated
MF→VeriMACI	£8,162	15.951	-	-	ext. dominated
chondrosphere→MF	£14,174	17.955	£8,412	2.077	£4,051
chondrosphere→ chondrosphere	£14,993	18.000	£819	0.045	£18,137
VeriMACI→MF	£20,595	18.261	-	-	ext. dominated
ChondroCelect→MF	£20,615	18.244	-	-	dominated
VeriMACI→ VeriMACI	£22,312	18.395	£7,319	0.395	£18,523
ChondroCelect→ ChondroCelect	£22,400	18.386	-	-	dominated

ICER: incremental cost effectiveness ratio; MF: microfracture; QALY: quality adjusted life year

❖ ***Is chondrosphere a cost-effective treatment?***

ERG exploratory analysis (1)

	Company	ERG changes
Comparators	MF→MF, MF→ACI, ACI→MF, ACI→ACI	MF, ACI→MF, ACI→ACI
Comparators 2 year probability of response	$1-(1-X)^{RR}$	X*RR
	[X=chondrosphere response rate from COWISI; RR=relative risks of comparators from NMA]	
Probability of response for 2nd repairs	√Response rate	Apply 2 year probability of response in 1 model cycle
Comparators probability of 2nd repairs	1 minus 2 year probabilities of response	Multiply chondrosphere probability of 2nd repair (1 minus 2 year probability of response) by comparators' relative risks of 2nd repair
Microfracture probability of 2nd repair	1.72%	Remove double halving of 2 year probability; 1.73%

ERG exploratory analysis (2)

	Company	ERG changes
Probability of moving from 2nd repair success to no further repair	Probability of moving from 1st repair success to no further repair	Use probability of 1st repair of same type
Microfracture QoL at 5 years	base case: QoL return to baseline values; sensitivity analysis: QoL gains maintained	2 analyses: QoL return to baseline values **and** QOL maintained at 5 year values indefinitely
Knee replacement to no further replacement QoL values	0.691 or 0.557	0.691 only
Costs of operations	Arthroscopy £734 Arthrotomy £1,065	Arthroscopy £870 Arthrotomy £2,396

❖ ***Which base case inputs are preferred?***

ERG base case deterministic results

	MF: QoL return to baseline value at 5 years			MF: QoL gains maintained at 5 years		
	Total Costs	Total QALYs	ICER	Total Costs	Total QALYs	ICER
MF	£5,043	15.779	-	£5,043	18.119	-
CHS→MF	£15,980	17.989	£4,949	£15,980	18.036	Dominated
CHS→CHS	£16,987	18.035	Ext. Dom.	£16,987	18.035	Dominated
VeriMACI→MF	£22,076	18.437	Ext. Dom.	£22,076	18.494	Ext. Dom.
CC→MF	£22,116	18.410	Dominated	£22,116	18.472	Dominated
VeriMACI→VeriMACI	£24,011	18.640	£12,336	£24,011	18.640	£36,425
CC→CC	£24,198	18.629	Dominated	£24,198	18.629	Dominated

CC: ChondroCelect, CHS: chondrosphere, ICER: incremental cost effectiveness ratio; MF: microfracture; QALY: quality adjusted life year

❖ ***Is chondrosphere a cost-effective treatment?***

ERG scenario analyses

Microfracture quality of life returns to baseline value at 5 years

- SA01: Pooling the microfracture response data across the 3 trials to yield an estimate of 70% and using the company NMA to provide estimates of 72% for chondrosphere, 88% for VeriMACI and 87% for ChondroCelect
- SA02: Applying the company revised estimates of the probability of response from clarification response #2
- SA03: No 2nd repairs
- SA04: A 2nd microfracture repair after 1st microfracture repair being possible

	Base	SA01	SA02	SA03	SA04
MF	..	..	..	..	..
CHS→MF	£4,949	£5,554	£5,030	n.a.	£4,791
CHS→CHS	Ext. Dom.	Ext. Dom.	Ext. Dom.	£4,360	Ext. Dom.
VeriMACI→MF	Ext. Dom.	£15,310	Ext. Dom.	n.a.	Ext. Dom.
CC→MF	Dominated	Dominated	Dominated	n.a.	Dominated
VeriMACI→ VeriMACI	£12,336	£15,177	£18,284	£12,180	£12,336
CC→CC	Dominated	Dominated	Dominated	Dominated	Dominated

CC: ChondroCelect, CHS: chondrosphere, ICER: incremental cost effectiveness ratio; MF: microfracture; QALY: quality adjusted life year

ERG scenario analyses
Microfracture quality of life maintained at 5 years

- SA01: Pooling the microfracture response data across the 3 trials to yield an estimate of 70% and using the company NMA to provide estimates of 72% for chondrosphere, 88% for VeriMACI and 87% for ChondroCelect
- SA02: Applying the company revised estimates of the probability of response from clarification response #2
- SA03: No 2nd repairs
- SA04: A 2nd microfracture repair after 1st microfracture repair being possible

	Base	SA01	SA02	SA03	SA04
MF	..	..	..	..	..
CHS→MF	Dominated	Dominated	Dominated	n.a.	Ext. Dom.
CHS→CHS	Dominated	Dominated	Dominated	Ext. Dom.	Dominated
VeriMACI→MF	Ext. Dom.	Ext. Dom.	Ext. Dom.	n.a.	Ext. Dom.
CC→MF	Dominated	Dominated	Dominated	n.a.	Dominated
VeriMACI→ VeriMACI	£36,425	£51,698	£71,489	£29,349	£20,601
CC→CC	Dominated	Dominated	Dominated	Dominated	Dominated

CC: ChondroCelect, CHS: chondrosphere, ICER: incremental cost effectiveness ratio; MF: microfracture; QALY: quality adjusted life year

ERG scenario analysis

Head-to-head comparison of chondrosphere with microfracture using response probabilities from COWISI

	MF vs CHS→CHS				MF vs CHS only			
	MF: all QoL gains lost at 5 years		MF: all QoL gains NOT lost at 5 years		MF: all QoL gains lost at 5 years		MF: all QoL gains NOT lost at 5 years	
	Costs	QALYs	Costs	QALYs	Costs	QALYs	Costs	QALYs
MF	£5,043	15.779	£5,043	18.119	£5,043	15.779	£5,043	18.119
CHS→ CHS or CHS only	£16,987	18.035	£16,987	18.035	£15,549	18.189	15,549	18.189
net	£11,944	2.256	£11,944	-0.084	£10,506	2.410	£10,506	0.070
ICER	£5,294		Dominated		£4,360		£150,506	

CHS: chondrosphere, ICER: incremental cost effectiveness ratio; MF: microfracture; QALY: quality adjusted life year

Innovation
Company comments

- Chondrosphere produces hyaline like cartilage; microfracture produces fibrocartilage (inferior)
- Treatment with chondrosphere is less invasive than other ACIs (implanted via arthroscopy, other ACIs – via arthrotomy)
- Does not use additional delivery mechanisms e.g. scaffolds of animal origin
- 100% autologous and additive free (no animal derivatives)

❖ ***Is chondrosphere innovative?***

Equality considerations

- Chondrosphere contains no animal derivatives nor additional delivery mechanisms of animal origin – therefore no patient exclusion based on ethical, moral or religious grounds
- Older people: data limited to patients up to 55 years; contraindications: advanced degeneration or osteoarthritis

❖ ***Are there any equality issues to consider?***

Key issues for discussion (1)

- Comparators:
  - Should traditional ACI be excluded from the decision problem?
  - Which treatment sequences are clinically relevant and most appropriate for decision making?
- Is chondrosphere clinically effective? For which lesion size? [COWISI: 1-4cm^2; Phase 2: 4-10cm^2]
  - COWISI non-inferiority design
  - Are the results from the network meta-analysis robust to infer clinical effectiveness and be used in the health economic modelling?
  - Is there any evidence to support the long term benefit of chondrosphere?
- Limitations of this model compared TA477
  - Model structure

Key issues for discussion (2)

- Concerns about transition probabilities and inputs
  - What is the most appropriate way of applying the treatment effectiveness estimates from the network meta-analysis to the health economic model?
- How should treatment waning for microfracture be modelled?
- Which base case (assumes microfracture QoL gains return to baseline level) is preferred: company's or ERG's?
- Innovation
- Equality issues

END OF PART 1